Clinical trial results:
A randomized, active-comparator-controlled, multicenter study to assess the safety and efficacy of different doses of BAY1213790 for the prevention of venous thromboembolism in patients undergoing elective primary total knee arthroplasty, open-label to treatment and observer-blinded to BAY1213790 doses.

Summary

EudraCT number	2016-002681-31
Trial protocol	ES LT CZ DE LV BG PL GR PT
Global end of trial date	02 January 2019

Results information

Result version number	v1 (current)
This version publication date	05 January 2020
First version publication date	05 January 2020

Trial information

Trial identification

Sponsor protocol code	BAY1213790/17664

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03276143
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, 51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 January 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 January 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and efficacy of different doses of BAY1213790 in comparison with those of enoxaparin in patients undergoing elective, primary, unilateral total knee arthroplasty (TKA).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

None

Evidence for comparator:

Yes

Actual start date of recruitment	21 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Czech Republic: 33
Country: Number of subjects enrolled	Greece: 87
Country: Number of subjects enrolled	Israel: 80
Country: Number of subjects enrolled	Latvia: 99
Country: Number of subjects enrolled	Lithuania: 124
Country: Number of subjects enrolled	Poland: 133
Country: Number of subjects enrolled	Bulgaria: 9
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Russian Federation: 49
Country: Number of subjects enrolled	South Africa: 41
Country: Number of subjects enrolled	Spain: 55
Country: Number of subjects enrolled	Ukraine: 90
Worldwide total number of subjects	813
EEA total number of subjects	552

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	317
From 65 to 84 years	489
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

The first visit of the first subject was on 21-Sep-2017, the last visit of the last subject was on 02-Jan-2019.

Pre-assignment

Screening details:

945 subjects were screened of whom 132 patients were screening failures. 813 patients were enrolled and randomized, of whom 790 received a drug (either BAY1213790 or comparators). 780 patients completed the treatment phase, 752 patients completed the post-treatment observation phase.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Enoxaparin (ENO)

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Enoxaparin sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Dose of 40 mg once daily from Day 1 to Day 15

Arm title	Apixaban (API)

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Apixaban
Investigational medicinal product code	
Other name	Eliquis
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dose of 2.5g mg twice daily from Day 2 to Day 15

Arm title	BAY1213790 0.3mg/kg (post-surgery)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Osocimab
Investigational medicinal product code	BAY1213790
Other name	Monoclonal antibody targeting FXIa
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single dose of 0.3 mg per kg body weight on Day 2 (post-surgery)

Arm title	BAY1213790 0.6mg/kg (post-surgery)

Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Osocimab
Investigational medicinal product code	BAY1213790
Other name	Monoclonal antibody targeting FXIa
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single dose of 0.6 mg per kg body weight on Day 2 (post-surgery)

Arm title	BAY1213790 1.2mg/kg (post-surgery)
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Osocimab
Investigational medicinal product code	BAY1213790
Other name	Monoclonal antibody targeting FXIa
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single dose of 1.2 mg per kg body weight on Day 2 (post-surgery)

Arm title	BAY1213790 1.8mg/kg (post-surgery)
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Osocimab
Investigational medicinal product code	BAY1213790
Other name	Monoclonal antibody targeting FXIa
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single dose of 1.8 mg per kg body weight on Day 2 (post-surgery)

Arm title	BAY1213790 0.3mg/kg (pre-surgery)
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Osocimab
Investigational medicinal product code	BAY1213790
Other name	Monoclonal antibody targeting FXIa
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single dose of 0.3 mg per kg body weight on Day 1 (pre-surgery)

Arm title	BAY1213790 1.8mg/kg (pre-surgery)
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Osocimab
Investigational medicinal product code	BAY1213790
Other name	Monoclonal antibody targeting FXIa
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single dose of 1.8 mg per kg body weight on Day 1 (pre-surgery)

Number of subjects in period 1	Enoxaparin (ENO)	Apixaban (API)	BAY1213790 0.3mg/kg (post-surgery)
Started	105	105	107
Treatment started	103	100	101
Completed	103	99	99
Not completed	2	6	8
Consent withdrawn by subject	1	3	2
Physician decision	-	1	-
Adverse event, non-fatal	1	1	3
Other reasons	-	1	3
Protocol deviation	-	-	-

Number of subjects in period 1	BAY1213790 0.6mg/kg (post-surgery)	BAY1213790 1.2mg/kg (post-surgery)	BAY1213790 1.8mg/kg (post-surgery)
Started	65	108	106
Treatment started	65	105	101
Completed	65	103	101
Not completed	0	5	5
Consent withdrawn by subject	-	3	2
Physician decision	-	-	-
Adverse event, non-fatal	-	2	1
Other reasons	-	-	-
Protocol deviation	-	-	2

Number of subjects in period 1	BAY1213790 0.3mg/kg (pre-	BAY1213790 1.8mg/kg (pre-
Started	109	108
Treatment started	107	108
Completed	105	105
Not completed	4	3
Consent withdrawn by subject	2	3
Physician decision	1	-
Adverse event, non-fatal	-	-
Other reasons	1	-
Protocol deviation	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Enoxaparin (ENO)
Reporting group description: -	
Reporting group title	Apixaban (API)
Reporting group description: -	
Reporting group title	BAY1213790 0.3mg/kg (post-surgery)
Reporting group description: -	
Reporting group title	BAY1213790 0.6mg/kg (post-surgery)
Reporting group description: -	
Reporting group title	BAY1213790 1.2mg/kg (post-surgery)
Reporting group description: -	
Reporting group title	BAY1213790 1.8mg/kg (post-surgery)
Reporting group description: -	
Reporting group title	BAY1213790 0.3mg/kg (pre-surgery)
Reporting group description: -	
Reporting group title	BAY1213790 1.8mg/kg (pre-surgery)
Reporting group description: -	

Reporting group values	Enoxaparin (ENO)	Apixaban (API)	BAY1213790 0.3mg/kg (post-surgery)
Number of subjects	105	105	107
Age Categorical			
All enrolled subjects			
Units: Subjects			
Age < 60 years	22	22	27
Age >= 60 years	83	83	80
Age Continuous			
All enrolled subjects			
Units: years			
arithmetic mean	66.4	65.9	65.9
standard deviation	± 8.6	± 8.2	± 8.5
Gender Categorical			
All enrolled subjects			
Units: Subjects			
Male	29	22	32
Female	76	83	75
Main indication for total knee arthroplasty (TKA)			
All enrolled subjects			
Units: Subjects			
Osteoarthritis	97	95	101
Rheumatoid arthritis	3	2	1
Fracture sequelae	1	1	0
Osteonecrosis	1	0	0
Other	1	3	0
TKA not performed	2	4	5

Body mass index			
All enrolled subjects			
Units: kg m-2			
arithmetic mean	32.72	32.74	32.20
standard deviation	± 5.73	± 5.67	± 5.19

Reporting group values	BAY1213790 0.6mg/kg (post-surgery)	BAY1213790 1.2mg/kg (post-surgery)	BAY1213790 1.8mg/kg (post-surgery)
Number of subjects	65	108	106
Age Categorical			
All enrolled subjects			
Units: Subjects			
Age < 60 years	15	24	17
Age >= 60 years	50	84	89
Age Continuous			
All enrolled subjects			
Units: years			
arithmetic mean	66.4	66.4	67.6
standard deviation	± 9.2	± 8.3	± 7.6
Gender Categorical			
All enrolled subjects			
Units: Subjects			
Male	20	21	33
Female	45	87	73
Main indication for total knee arthroplasty (TKA)			
All enrolled subjects			
Units: Subjects			
Osteoarthritis	63	104	97
Rheumatoid arthritis	1	1	1
Fracture sequelae	1	0	3
Osteonecrosis	0	0	1
Other	0	0	0
TKA not performed	0	3	4
Body mass index			
All enrolled subjects			
Units: kg m-2			
arithmetic mean	31.72	33.89	31.94
standard deviation	± 5.45	± 5.75	± 5.31

Reporting group values	BAY1213790 0.3mg/kg (pre-	BAY1213790 1.8mg/kg (pre-	Total
Number of subjects	109	108	813
Age Categorical			
All enrolled subjects			
Units: Subjects			
Age < 60 years	21	15	163
Age >= 60 years	88	93	650
Age Continuous			
All enrolled subjects			
Units: years			
arithmetic mean	66.1	67.7	

standard deviation	± 8.2	± 7.3	-

Gender Categorical			
All enrolled subjects			
Units: Subjects			
Male	25	28	210
Female	84	80	603
Main indication for total knee arthroplasty (TKA)			
All enrolled subjects			
Units: Subjects			
Osteoarthritis	102	101	760
Rheumatoid arthritis	0	1	10
Fracture sequelae	0	0	6
Osteonecrosis	0	0	2
Other	4	5	13
TKA not performed	3	1	22
Body mass index			
All enrolled subjects			
Units: kg m-2			
arithmetic mean	32.26	33.62	
standard deviation	± 6.23	± 5.92	-

Subject analysis sets

Subject analysis set title	Safety set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received at least one dose of study drug and had total knee arthroplasty (TKA) surgery

Subject analysis set title	Per Protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who received at least one dose of study drug, had a valid venography or an objectively confirmed symptomatic venous thromboembolism before Day 15 and did not have an important deviation from protocol or validity finding

Reporting group values	Safety set (SAF)	Per Protocol Set (PPS)	
Number of subjects	787	600	
Age Categorical			
All enrolled subjects			
Units: Subjects			
Age < 60 years	153	122	
Age >= 60 years	634	478	
Age Continuous			
All enrolled subjects			
Units: years			
arithmetic mean	66.6	66.5	
standard deviation	± 8.2	± 8.2	

Gender Categorical			
All enrolled subjects			
Units: Subjects			
Male	204	164	
Female	583	436	
Main indication for total knee arthroplasty (TKA)			
All enrolled subjects			
Units: Subjects			
Osteoarthritis	756	583	
Rheumatoid arthritis	10	7	
Fracture sequelae	6	4	
Osteonecrosis	2	2	
Other	13	4	
TKA not performed	0	0	
Body mass index			
All enrolled subjects			
Units: kg m-2			
arithmetic mean	32.64	32.48	
standard deviation	± 5.68	± 5.68	

End points

End points reporting groups

Reporting group title	Enoxaparin (ENO)
Reporting group description: -	
Reporting group title	Apixaban (API)
Reporting group description: -	
Reporting group title	BAY1213790 0.3mg/kg (post-surgery)
Reporting group description: -	
Reporting group title	BAY1213790 0.6mg/kg (post-surgery)
Reporting group description: -	
Reporting group title	BAY1213790 1.2mg/kg (post-surgery)
Reporting group description: -	
Reporting group title	BAY1213790 1.8mg/kg (post-surgery)
Reporting group description: -	
Reporting group title	BAY1213790 0.3mg/kg (pre-surgery)
Reporting group description: -	
Reporting group title	BAY1213790 1.8mg/kg (pre-surgery)
Reporting group description: -	
Subject analysis set title	Safety set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received at least one dose of study drug and had total knee arthroplasty (TKA) surgery	
Subject analysis set title	Per Protocol Set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients who received at least one dose of study drug, had a valid venography or an objectively confirmed symptomatic venous thromboembolism before Day 15 and did not have an important deviation from protocol or validity finding	

Primary: Incidence of the composite efficacy endpoint

End point title	Incidence of the composite efficacy endpoint
End point description:	
Incidence of the composite endpoint consisting of asymptomatic deep vein thrombosis (DVT) detected by mandatory bilateral venography, objectively confirmed symptomatic DVT, non-fatal pulmonary embolism (PE), fatal PE and unexplained death for which PE cannot be excluded from randomization up to Day 15	
End point type	Primary
End point timeframe:	
Up to 15 days	

End point values	Enoxaparin (ENO)	Apixaban (API)	BAY1213790 0.3mg/kg (post-surgery)	BAY1213790 0.6mg/kg (post-surgery)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	83	76	51
Units: Number of subjects				
Primary efficacy endpoint	20	12	18	8
- Asymptomatic deep vein thrombosis (DVT)	20	11	18	7

- Symptomatic deep vein thrombosis (DVT)	1	1	1	1
- Non-fatal pulmonary embolism (PE)	0	0	0	0
- Fatal pulmonary embolism (PE)	0	0	0	0
-Unexplained death for which PE cannot be excluded	0	0	0	0

End point values	BAY1213790 1.2mg/kg (post-surgery)	BAY1213790 1.8mg/kg (post-surgery)	BAY1213790 0.3mg/kg (pre-surgery)	BAY1213790 1.8mg/kg (pre-surgery)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	78	77	80
Units: Number of subjects				
Primary efficacy endpoint	13	14	23	9
- Asymptomatic deep vein thrombosis (DVT)	13	14	22	9
- Symptomatic deep vein thrombosis (DVT)	1	2	1	0
- Non-fatal pulmonary embolism (PE)	0	0	0	0
- Fatal pulmonary embolism (PE)	0	0	0	0
-Unexplained death for which PE cannot be excluded	0	0	0	0

End point values	Per Protocol Set (PPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	117			
Units: Number of subjects				
Primary efficacy endpoint	117			
- Asymptomatic deep vein thrombosis (DVT)	114			
- Symptomatic deep vein thrombosis (DVT)	8			
- Non-fatal pulmonary embolism (PE)	0			
- Fatal pulmonary embolism (PE)	0			
-Unexplained death for which PE cannot be excluded	0			

Statistical analyses

Statistical analysis title	Difference between BAY1213790 to enoxaparin_1
Statistical analysis description:	
Difference in proportion of patients with the primary efficacy endpoint between 0.3 mg BAY1213790 post-surgery group and enoxaparin	
Comparison groups	Enoxaparin (ENO) v BAY1213790 0.3mg/kg (post-surgery) v Per Protocol Set (PPS)

Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1385
Method	Asymptotic Wald test
Parameter estimate	Point estimate (%)
Point estimate	2.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	-8.9
upper limit	14.2

Statistical analysis title	Difference between BAY1213790 to enoxaparin_2
Statistical analysis description:	
Difference in proportion of patients with the primary efficacy endpoint between 0.6 mg BAY1213790 post-surgery group and enoxaparin	
Comparison groups	Enoxaparin (ENO) v BAY1213790 0.6mg/kg (post-surgery) v Per Protocol Set (PPS)
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0147
Method	Asymptotic Wald test
Parameter estimate	Point estimate (%)
Point estimate	10.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.2
upper limit	22.4

Statistical analysis title	Difference between BAY1213790 to enoxaparin_3
Statistical analysis description:	
Difference in proportion of patients with the primary efficacy endpoint between 1.2 mg BAY1213790 post-surgery group and enoxaparin	
Comparison groups	Enoxaparin (ENO) v BAY1213790 1.2mg/kg (post-surgery) v Per Protocol Set (PPS)
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0117
Method	Asymptotic Wald test
Parameter estimate	Point estimate (%)
Point estimate	9.9

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.9
upper limit	20.6

Statistical analysis title	Difference between BAY1213790 to enoxaparin_4
Statistical analysis description:	
Difference in proportion of patients with the primary efficacy endpoint between 1.8 mg BAY1213790 post-surgery group and enoxaparin	
Comparison groups	Enoxaparin (ENO) v BAY1213790 1.8mg/kg (post-surgery) v Per Protocol Set (PPS)
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0224
Method	Asymptotic Wald test
Parameter estimate	Point estimate (%)
Point estimate	8.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.6
upper limit	19.3

Statistical analysis title	Difference between BAY1213790 to enoxaparin_5
Statistical analysis description:	
Difference in proportion of patients with the primary efficacy endpoint between 0.3 mg BAY1213790 pre-surgery group and enoxaparin	
Comparison groups	Enoxaparin (ENO) v BAY1213790 0.3mg/kg (pre-surgery) v Per Protocol Set (PPS)
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4211
Method	Asymptotic Wald test
Parameter estimate	Point estimate (%)
Point estimate	-3.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	-15.5
upper limit	8.4

Statistical analysis title	Difference between BAY1213790 to enoxaparin_6

Statistical analysis description:

Difference in proportion of patients with the primary efficacy endpoint between 1.8 mg BAY1213790 pre-surgery group and enoxaparin

Comparison groups	Enoxaparin (ENO) v BAY1213790 1.8mg/kg (pre-surgery) v Per Protocol Set (PPS)
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0073
Method	Asymptotic Wald test
Parameter estimate	Point estimate (%)
Point estimate	15.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	4.9
upper limit	25.2

Primary: Incidence of the composite safety endpoint

End point title	Incidence of the composite safety endpoint[1]

End point description:

Incidence of the composite of major and clinically relevant non-major bleeding events from randomization to Day 15

End point type	Primary

End point timeframe:

Up to 15 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The comparison between the BAY1213790 arms and apixaban for primary efficacy as well as all safety analyses were pre-planned to be performed descriptively.

End point values	Enoxaparin (ENO)	Apixaban (API)	BAY1213790 0.3mg/kg (post-surgery)	BAY1213790 0.6mg/kg (post-surgery)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	100	102	65
Units: Number of subjects				
Primary efficacy endpoint	6	2	2	0
Major bleeding	0	0	0	0
Clinically relevant non-major bleeding	6	2	2	0

End point values	BAY1213790 1.2mg/kg (post-surgery)	BAY1213790 1.8mg/kg (post-surgery)	BAY1213790 0.3mg/kg (pre-surgery)	BAY1213790 1.8mg/kg (pre-surgery)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	101	106	107
Units: Number of subjects				
Primary efficacy endpoint	1	3	2	5

Major bleeding	0	0	0	1
Clinically relevant non-major bleeding	1	3	2	4

End point values	Safety set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	787			
Units: Number of subjects				
Primary efficacy endpoint	21			
Major bleeding	1			
Clinically relevant non-major bleeding	20			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of the composite secondary efficacy endpoint

End point title	Incidence of the composite secondary efficacy endpoint

End point description:

Incidence of the composite endpoint of symptomatic deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), fatal PE and unexplained death for which PE cannot be excluded from randomization up to Day 157 or objectively confirmed asymptomatic DVT from randomization up to Day 15

End point type	Secondary

End point timeframe:

Up to 157 days

End point values	Enoxaparin (ENO)	Apixaban (API)	BAY1213790 0.3mg/kg (post-surgery)	BAY1213790 0.6mg/kg (post-surgery)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	83	76	51
Units: Number of subjects				
Secondary efficacy endpoint	20	13	18	8
-Asymptomatic deep vein thrombosis (DVT) to Day 15	20	11	18	7
-Symptomatic deep vein thrombosis (DVT)	1	1	1	1
-Non-fatal pulmonary embolism (PE)	0	1	0	0
-Fatal pulmonary embolism (PE)	0	0	0	0
-Unexplained death for which PE cannot be excluded	0	0	0	0

End point values	BAY1213790 1.2mg/kg	BAY1213790 1.8mg/kg	BAY1213790 0.3mg/kg (pre-	BAY1213790 1.8mg/kg (pre-

	(post-surgery)	(post-surgery)	surgery)	surgery)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	78	77	80
Units: Number of subjects				
Secondary efficacy endpoint	13	14	24	9
-Asymptomatic deep vein thrombosis (DVT) to Day 15	13	14	22	9
-Symptomatic deep vein thrombosis (DVT)	1	2	2	0
-Non-fatal pulmonary embolism (PE)	1	0	0	1
-Fatal pulmonary embolism (PE)	0	0	0	0
-Unexplained death for which PE cannot be excluded	0	0	0	0

End point values	Per Protocol Set (PPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	600			
Units: Number of subjects				
Secondary efficacy endpoint	119			
-Asymptomatic deep vein thrombosis (DVT) to Day 15	114			
-Symptomatic deep vein thrombosis (DVT)	9			
-Non-fatal pulmonary embolism (PE)	3			
-Fatal pulmonary embolism (PE)	0			
-Unexplained death for which PE cannot be excluded	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of the composite secondary safety endpoint

End point title	Incidence of the composite secondary safety endpoint

End point description:

Incidence of composite of major and clinically relevant non-major bleeding from randomization to Day 157

End point type	Secondary

End point timeframe:

Up to 157 days

End point values	Enoxaparin (ENO)	Apixaban (API)	BAY1213790 0.3mg/kg (post-surgery)	BAY1213790 0.6mg/kg (post-surgery)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	100	102	65
Units: Number of subjects				
At least one secondary safety event	7	2	3	0
- Major bleeding	0	0	0	0
- Clinically relevant non-Major bleeding	7	2	3	0

End point values	BAY1213790 1.2mg/kg (post-surgery)	BAY1213790 1.8mg/kg (post-surgery)	BAY1213790 0.3mg/kg (pre-surgery)	BAY1213790 1.8mg/kg (pre-surgery)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	101	106	107
Units: Number of subjects				
At least one secondary safety event	1	3	2	6
- Major bleeding	0	0	0	2
- Clinically relevant non-Major bleeding	1	3	2	4

End point values	Safety set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	787			
Units: Number of subjects				
At least one secondary safety event	24			
- Major bleeding	2			
- Clinically relevant non-Major bleeding	22			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first drug application up to Day 157	
Adverse event reporting additional description:	
3 of 790 treated patients were excluded from SAF, because TKA was not performed.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	Enoxaparin 40 mg OD
Reporting group description:	
Patients with TKA who received Enoxaparin sodium once daily starting either before or after TKA until venography	
Reporting group title	Apixaban 2.5 mg BID
Reporting group description:	
Patients with TKA who received apixaban twice daily starting after TKA until venography	
Reporting group title	0.3 mg/kg BAY1213790 post-surgery
Reporting group description:	
Patients with TKA who received 0.3 mg BAY1213790 once the day after TKA	
Reporting group title	0.6 mg/kg BAY1213790 post-surgery
Reporting group description:	
Patients with TKA who received 0.6 mg BAY1213790 once the day after TKA	
Reporting group title	1.8 mg/kg BAY1213790 post-surgery
Reporting group description:	
Patients with TKA who received 1.8 mg BAY1213790 once the day after TKA	
Reporting group title	1.2 mg/kg BAY1213790 post-surgery
Reporting group description:	
Patients with TKA who received 1.2 mg BAY1213790 once the day after TKA	
Reporting group title	0.3 mg/kg BAY1213790 pre-surgery
Reporting group description:	
Patients with TKA who received 0.3 mg BAY1213790 once the day before TKA	
Reporting group title	1.8 mg/kg BAY1213790 pre-surgery
Reporting group description:	
Patients with TKA who received 1.8 mg BAY1213790 once the day before TKA	

Serious adverse events	Enoxaparin 40 mg OD	Apixaban 2.5 mg BID	0.3 mg/kg BAY1213790 post-surgery
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 102 (10.78%)	5 / 100 (5.00%)	9 / 102 (8.82%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Basal cell carcinoma			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hyperaemia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis superficial			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 102 (0.98%)	1 / 100 (1.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Knee arthroplasty			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Physiotherapy			
subjects affected / exposed	2 / 102 (1.96%)	0 / 100 (0.00%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rehabilitation therapy			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 102 (0.98%)	1 / 100 (1.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural fistula			

subjects affected / exposed	1 / 102 (0.98%)	1 / 100 (1.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incision site inflammation			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural swelling			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	2 / 102 (1.96%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia Alzheimer's type			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pemphigus			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			

subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint contracture			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint effusion			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint stiffness			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint range of motion decreased			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			

subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			

subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device site joint infection			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	0.6 mg/kg BAY1213790 post-surgery	1.8 mg/kg BAY1213790 post-surgery	1.2 mg/kg BAY1213790 post-surgery
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 65 (6.15%)	7 / 101 (6.93%)	10 / 104 (9.62%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 65 (0.00%)	1 / 101 (0.99%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hyperaemia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis superficial			

subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 101 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Knee arthroplasty			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Physiotherapy			
subjects affected / exposed	1 / 65 (1.54%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rehabilitation therapy			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	0 / 65 (0.00%)	1 / 101 (0.99%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	0 / 65 (0.00%)	1 / 101 (0.99%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural fistula			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incision site inflammation			
subjects affected / exposed	0 / 65 (0.00%)	1 / 101 (0.99%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural swelling			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	0 / 65 (0.00%)	1 / 101 (0.99%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia Alzheimer's type			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			

subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pemphigus			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint contracture			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint effusion			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint stiffness			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lumbar spinal stenosis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint range of motion decreased			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 65 (0.00%)	2 / 101 (1.98%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			

subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 101 (0.99%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	0 / 65 (0.00%)	1 / 101 (0.99%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device site joint infection			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	2 / 104 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	0.3 mg/kg BAY1213790 pre-surgery	1.8 mg/kg BAY1213790 pre-surgery	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 106 (4.72%)	9 / 107 (8.41%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hyperaemia			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 106 (1.89%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Knee arthroplasty			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Physiotherapy			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rehabilitation therapy			

subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			

subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fistula			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site inflammation			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural swelling			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			

subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pemphigus			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			

subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint contracture			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint stiffness			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint range of motion decreased			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			

subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site joint infection			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Enoxaparin 40 mg OD	Apixaban 2.5 mg BID	0.3 mg/kg BAY1213790 post-surgery
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 102 (50.00%)	25 / 100 (25.00%)	42 / 102 (41.18%)
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 102 (5.88%)	0 / 100 (0.00%)	2 / 102 (1.96%)
occurrences (all)	6	0	2
Haemoglobin decreased			
subjects affected / exposed	18 / 102 (17.65%)	4 / 100 (4.00%)	3 / 102 (2.94%)
occurrences (all)	18	4	3
Platelet count decreased			
subjects affected / exposed	2 / 102 (1.96%)	1 / 100 (1.00%)	0 / 102 (0.00%)
occurrences (all)	2	1	0
Injury, poisoning and procedural complications			

Subcutaneous haematoma			
subjects affected / exposed	3 / 102 (2.94%)	4 / 100 (4.00%)	9 / 102 (8.82%)
occurrences (all)	3	4	11
Post procedural haemorrhage			
subjects affected / exposed	6 / 102 (5.88%)	4 / 100 (4.00%)	3 / 102 (2.94%)
occurrences (all)	7	4	3
Incision site haemorrhage			
subjects affected / exposed	1 / 102 (0.98%)	3 / 100 (3.00%)	4 / 102 (3.92%)
occurrences (all)	1	3	4
Procedural pain			
subjects affected / exposed	10 / 102 (9.80%)	1 / 100 (1.00%)	5 / 102 (4.90%)
occurrences (all)	10	1	6
Post procedural swelling			
subjects affected / exposed	5 / 102 (4.90%)	3 / 100 (3.00%)	4 / 102 (3.92%)
occurrences (all)	5	3	4
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	20 / 102 (19.61%)	13 / 100 (13.00%)	19 / 102 (18.63%)
occurrences (all)	20	14	19
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 102 (6.86%)	0 / 100 (0.00%)	6 / 102 (5.88%)
occurrences (all)	7	0	6
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 102 (3.92%)	1 / 100 (1.00%)	4 / 102 (3.92%)
occurrences (all)	5	1	4
Nausea			
subjects affected / exposed	5 / 102 (4.90%)	1 / 100 (1.00%)	0 / 102 (0.00%)
occurrences (all)	5	1	0
Vomiting			
subjects affected / exposed	3 / 102 (2.94%)	2 / 100 (2.00%)	1 / 102 (0.98%)
occurrences (all)	3	2	1

Non-serious adverse events	0.6 mg/kg BAY1213790 post-surgery	1.8 mg/kg BAY1213790 post-surgery	1.2 mg/kg BAY1213790 post-surgery
Total subjects affected by non-serious adverse events			

subjects affected / exposed	25 / 65 (38.46%)	31 / 101 (30.69%)	38 / 104 (36.54%)
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 65 (3.08%)	1 / 101 (0.99%)	4 / 104 (3.85%)
occurrences (all)	2	1	4
Haemoglobin decreased			
subjects affected / exposed	1 / 65 (1.54%)	6 / 101 (5.94%)	8 / 104 (7.69%)
occurrences (all)	1	6	8
Platelet count decreased			
subjects affected / exposed	0 / 65 (0.00%)	1 / 101 (0.99%)	0 / 104 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Subcutaneous haematoma			
subjects affected / exposed	4 / 65 (6.15%)	4 / 101 (3.96%)	3 / 104 (2.88%)
occurrences (all)	4	4	3
Post procedural haemorrhage			
subjects affected / exposed	1 / 65 (1.54%)	2 / 101 (1.98%)	1 / 104 (0.96%)
occurrences (all)	1	2	1
Incision site haemorrhage			
subjects affected / exposed	2 / 65 (3.08%)	3 / 101 (2.97%)	2 / 104 (1.92%)
occurrences (all)	2	3	2
Procedural pain			
subjects affected / exposed	2 / 65 (3.08%)	2 / 101 (1.98%)	4 / 104 (3.85%)
occurrences (all)	2	2	5
Post procedural swelling			
subjects affected / exposed	2 / 65 (3.08%)	4 / 101 (3.96%)	2 / 104 (1.92%)
occurrences (all)	2	4	2
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	8 / 65 (12.31%)	12 / 101 (11.88%)	13 / 104 (12.50%)
occurrences (all)	8	12	13
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 65 (10.77%)	0 / 101 (0.00%)	6 / 104 (5.77%)
occurrences (all)	7	0	6
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	3 / 65 (4.62%)	2 / 101 (1.98%)	3 / 104 (2.88%)
occurrences (all)	3	2	3
Nausea			
subjects affected / exposed	0 / 65 (0.00%)	0 / 101 (0.00%)	2 / 104 (1.92%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	1 / 65 (1.54%)	0 / 101 (0.00%)	3 / 104 (2.88%)
occurrences (all)	1	0	3

Non-serious adverse events	0.3 mg/kg BAY1213790 pre-surgery	1.8 mg/kg BAY1213790 pre-surgery	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 106 (56.60%)	74 / 107 (69.16%)	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 106 (1.89%)	1 / 107 (0.93%)	
occurrences (all)	2	1	
Haemoglobin decreased			
subjects affected / exposed	19 / 106 (17.92%)	21 / 107 (19.63%)	
occurrences (all)	19	21	
Platelet count decreased			
subjects affected / exposed	2 / 106 (1.89%)	8 / 107 (7.48%)	
occurrences (all)	2	8	
Injury, poisoning and procedural complications			
Subcutaneous haematoma			
subjects affected / exposed	2 / 106 (1.89%)	3 / 107 (2.80%)	
occurrences (all)	2	3	
Post procedural haemorrhage			
subjects affected / exposed	9 / 106 (8.49%)	14 / 107 (13.08%)	
occurrences (all)	9	14	
Incision site haemorrhage			
subjects affected / exposed	5 / 106 (4.72%)	7 / 107 (6.54%)	
occurrences (all)	5	8	
Procedural pain			

subjects affected / exposed	28 / 106 (26.42%)	39 / 107 (36.45%)	
occurrences (all)	29	40	
Post procedural swelling			
subjects affected / exposed	10 / 106 (9.43%)	10 / 107 (9.35%)	
occurrences (all)	10	11	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	24 / 106 (22.64%)	13 / 107 (12.15%)	
occurrences (all)	24	13	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 106 (3.77%)	0 / 107 (0.00%)	
occurrences (all)	5	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 106 (7.55%)	14 / 107 (13.08%)	
occurrences (all)	8	14	
Nausea			
subjects affected / exposed	6 / 106 (5.66%)	4 / 107 (3.74%)	
occurrences (all)	6	4	
Vomiting			
subjects affected / exposed	3 / 106 (2.83%)	7 / 107 (6.54%)	
occurrences (all)	3	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2018	This global amendment comprised a modification of the randomization scheme to prevent unbalanzed arms, prohibited prior and concomittant medications (monoclonal antibodies not allowed) and inclusion criteria (pregancy test).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There was no adjustment for multiplicity for comparisons between osocimab and comparators groups. The study was only powered for the comparison of osocimab with enoxaparin, thus no statistics is provided for apixaban and all safety endpoints.

Notes: