Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix: Outcome Definitions

Assessment of Deep Vein Thrombosis (DVT) by Venography

The overall objective is to categorize each patient as:

(1) having no DVT

(2) having DVT

(3) nonevaluable for DVT.

Adjudication of venography involves the assessment of two regions – proximal (iliac, common femoral, femoral, deep femoral, and popliteal veins) and distal (calf, peroneal, posterior tibial, and anterior tibial veins, up to and including the point of trifurcation of the calf vein) – in each leg as:

(i) constant intra-luminal filling defect (DVT)

An area of reduced, or absent filling at least partially surrounded with contrast medium, which is constant in more than one film.

OR

Lack of filling in a vessel in which there is a cut-off that has the configuration of a thrombus and in which filling of that vessel is seen more proximally.

(ii) normal

All deep veins are visualized and there is no DVT.

(iii) indeterminate.

Lack of filling of a region of the deep vein system, either proximal or distal, without the presence of a DVT elsewhere in the same region.

NOTE: Failure to visualize the muscular veins of the thigh (deep femoral) or the anterior tibial veins of the calf does not cause a venogram to be classified as indeterminate.

A patient would be classified as:

(1) having no DVT: if the distal and proximal veins in both legs are normal

(2) having DVT: if any of the distal or proximal veins in either leg have a DVT

(3) nonevaluable for DVT: if neither (1) nor (2) is satisfied.

Presence and location of a DVT will be recorded on the central venography assessment form.

Suspected Venous Thromboembolism (VTE)

VTE is

EITHER

Symptoms of pulmonary embolism (PE) with one of the following findings.

- A (new) intraluminal filling defect in (sub)segmental or more proximal branches on spiral computerized tomography (CT) scan.
- A (new) intraluminal filling defect or an extension of an existing defect, or a new sudden cut-off of vessels of more than 2.5 mm in diameter on the pulmonary angiogram.
- A (new) perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scintigraphy.
- Inconclusive spiral CT, pulmonary angiography, or lung scintigraphy with demonstration of DVT in the lower extremities by compression ultrasound or venography.
- Fatal PE based on autopsy or objective diagnostic testing before death.
- Death that cannot be attributed to a documented cause and for which PE cannot be ruled out (unexplained death).

OR

Symptoms of DVT with one of the following findings.

In the absence of previous DVT investigations at baseline, diagnosis of suspected DVT requires the following.

- A noncompressible venous segment on ultrasonography. An intraluminal filling defect on venography, CT scan, or magnetic resonance venography.

If there were previous DVT investigations at baseline, diagnosis of suspected DVT requires one or both of the following.

- Abnormal compression ultrasound where compression had been normal.
- A new intraluminal filling defect, or an extension of nonvisualization of veins in the presence of a sudden cut-off on venography CT scan or MR venography.

Deaths

For all patients who died during the study, the Central Independent Adjudication Committee (CIAC) will assign the cause of death to one of the following.

- Cardiovascular (CV) death.
    - Acute myocardial infarction.
    - Sudden cardiac death.
    - Heart failure.
    - Stroke.
    - Cerebrovascular procedure.
    - Cerebrovascular hemorrhage.
    - Pulmonary embolism.

    - Other CV death, specified.
- Non-CV death.
    - Pulmonary.
    - Gastrointestinal.
    - Infection (including sepsis).
    - Inflammatory/immune (including autoimmune).
    - Non-CV hemorrhage.
    - Malignancy.
    - Other non-CV death, specified.
- Death, undetermined.
    - Unexplained death; PE cannot be ruled out.

For an adjudicated mortality event when the cause of death is adjudicated as PE or bleeding, the adjudication committee will automatically perform an additional adjudication for the specific event (VTE or bleeding) even if the investigator submitted only a mortality dossier. In cases in which the cause of death is determined to be due to VTE or bleeding, enough information should exist within the mortality dossier to make that determination. In some cases of VTE-related death, for instance when unexplained death and PE cannot be ruled out, the cause of death will be determined to be due to PE without objective evidence for PE. In these cases, only the mortality paper central assessment form would be enough unless the site had already sent in a suspected PE dossier.

Bleeding Events

All bleeding events will be classified according to the International Society of Thrombosis and Haemostasis (ISTH) criteria as major bleeding, clinically relevant nonmajor (CRNM) bleeding, minor bleeding, or no bleeding.

Major bleeding is defined as one of the following.

- Bleeding that contributed to death.
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, intramuscular with compartment syndrome, or intraarticular (operated joint excluded).
- Extra surgical site bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells, with temporal association within 24–48 h of the bleeding.
- Surgical site bleeding that requires a second intervention (open, arthroscopic, endovascular), or causing a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or wound healing, resulting in prolonged hospitalization or deep wound infection.
- Surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability. There should be an associated fall in hemoglobin level of at least 2 g/dL (1.24 mmol/L), or transfusion, indicated by the bleeding, of at least two units of whole blood or red cells, with temporal association within 24 h of the bleeding.

A CRNM bleed is an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following.

- Hospital admission for bleeding.
- Physician-guided medical or surgical treatment for bleeding.
- Change in antithrombotic therapy (including interruption or discontinuation of study drug).

All other overt bleeding events not meeting the criteria for CRNM bleeding will be classified as minor bleeding.

When assessing the clinical relevance of bleeding events for patients in this study (for instance when classifying these events as trivial, CRNM, or major), the specific conditions of the surgical intervention and associated medical acts must be considered. Major orthopedic surgery leads, by definition, to bleeding manifestations that are normal for the procedure. The following applies to patients with knee replacement surgery.

- Normal blood loss during surgery is between 250 ml and 600 ml, translating (depending on the weight of the patient) to a hemoglobin (Hb) drop of 1 to 2.5 g/dL. The assessment of blood loss during surgery (e.g. by weighing bandages and tampons) is notorious for underestimation.
- Normal, bloody discharge after surgery in drains placed during surgery in the surgical wound area varies between 100 and 500 ml, translating to a Hb drop of 0.5 to 1.0 g/dL.
- Normal bruising around the surgical incision usually covers an area of 10 to 50 cm^2.

Therefore, in general, only bleeding that exceeds the expectations of normal by the treating physician – excessive bleeding/drainage/bruising – should be considered an overt bleeding event.

In addition, fluids given to the patient during the anesthetic procedure usually result in hemodilution, causing another drop in Hb of 0.5 to 1.0 g/dL.

Especially in cases when the patient has given his own blood before surgery, the threshold for returning this blood (autologous transfusion) is much lower than for the ‘usual’ blood transfusions.

Hence, especially for bleeding occurring in the period immediately following surgery, the criteria for ISTH major bleeding should be applied with clinical acumen, and it needs to be taken into account whether the reported bleeding is so severe that it, in itself, could have caused the observed drop in Hb.

In addition, for no bleeding in surgical patients, who usually bleed during surgery, have a bit of bloody drainage from the surgical area, and some bruising around the surgical wound, the criteria are the absence of excessive bleeding during surgery, excessive bruising around the surgical wound, and excessive drainage from the surgical wound, as assessed by the attending physician/investigator, or the absence of any other bleeding outside the surgical area.

Conventions for review of multiple bleeding events in an individual.

- Recurrent events that occur on the same day count as a single event, and are classified based on the event with the highest severity (i.e. major > CRNM > minor).
- Classification of events that occur on separate days.
    - Recurrent events at different sites will be classified as new events.
    - Recurrent events at the same site that occur with an increased severity will be classified as new events.
    - Recurrent events at the same site with the same or lower severity are usually considered separate events. However, depending on description details, they may be considered as one event.

SUPPLEMENTAL TABLES AND FIGURES

eTable 1: Baseline characteristics by validity of venography at 10 to 13 days postoperatively in all patients who received at least one dose of study medication.[a]

	Venography valid (n = 611)	**Venography not valid (n = 176)**
Age, years	66.5 (8.3)	66.9 (7.7)
Female sex, no. (%)	444 (72.7)	139 (79.0)
Weight, kg	87.2 (16.5)	86.5 (16.0)
Body mass index, kg/m^2	32.5 (5.7)	33.2 (5.7)

[a]Values are presented as mean (SD) unless stated otherwise.

eTable 2: Sensitivity analysis of the primary efficacy outcome in the modified intention-to-treat population.[a]

Outcome	Postoperative osocimab				Preoperative osocimab		Enoxaparin (n = 77)	Apixaban (n = 84)
	0.3 mg/kg (n = 78)	0.6 mg/kg (n = 53)	1.2 mg/kg (n = 81)	1.8 mg/kg (n = 81)	0.3 mg/kg (n = 77)	1.8 mg/kg (n = 80)		
Primary outcome, no. (% [90% CI])[b]	18 (23.1 [15.5 to 32.3])	8 (15.1 [7.7 to 25.6])	13 (16.0 [9.8 to 24.3])	14 (17.3 [10.8 to 25.7])	23 (29.9 [21.4 to 39.6])	9 (11.3 [6.0 to 18.8])	20 (26.0 [17.9 to 35.5])	12 (14.3 [8.5 to 22.1])
Noninferiority of osocimab vs enoxaparin, % (1-sided 95% CI)								
Risk difference	2.9 (–8.5 to ∞)	10.9 (–0.7 to ∞)	9.9 (–0.7 to ∞)	8.7 (–2.0 to ∞)	–3.9 (–15.8 to ∞)	14.7 (4.7 to ∞)		
P value	.13	.01	.01	.02	.44	<.001		
Superiority of osocimab vs enoxaparin, % (2-sided 90% CI)[c]								
Risk difference	2.9 (–8.5 to 14.3)	10.9 (–0.7 to 22.4)	9.9 (–0.7 to 20.5)	8.7 (–2.0 to 19.4)	–3.9 (–15.8 to 8.0)	14.7 (4.7 to 24.8)		
P value		.06	.06	.09		.008		
Exploratory comparison of osocimab vs apixaban, % (90% CI)[d]								
Risk difference	–8.8 (–18.8 to 1.3)	–0.8 (–11.0 to 9.4)	–1.8 (–11.0 to 7.4)	–3.0 (–12.3 to 6.3)	–15.6 (–26.2 to –5.0)	3.0 (–5.5 to 11.6)		
Components of the primary efficacy outcome								
Asymptomatic DVT	18 (23.1)	7 (13.2)	13 (16.0)	14 (17.3)	22 (28.6)	9 (11.3)	20 (26.0)	11 (13.1)
Symptomatic DVT	1 (1.3)	1 (1.9)	1 (1.2)	2 (2.5)	1 (1.3)	0	1 (1.3)	1 (1.2)
Proximal DVT[e]	2 (2.6)	3 (5.7)	3 (3.7)	3 (3.7)	5 (6.5)	2 (2.5)	3 (3.9)	2 (2.4)
Distal DVT[e]	18 (23.1)	8 (15.1)	13 (16.0)	13 (16.0)	24 (31.2)	9 (11.3)	19 (24.7)	12 (14.3)

CI, confidence interval, DVT, deep vein thrombosis.

[a]The sensitivity analysis was performed in the modified intention-to-treat population, which comprised all patients who received at least one dose of study medication and who could be evaluated for the primary outcome.

[b]The primary efficacy outcome was the incidence of a composite of asymptomatic and symptomatic venous thromboembolism up to 10 to 13 days postoperatively, which corresponded to study days 12 to 15. None of the patients had pulmonary embolism and there were no deaths.

[c]A hierarchical scheme was used in which testing for superiority of osocimab vs enoxaparin was permitted if noninferiority was achieved.

[d]No statistical hypothesis was defined for the comparison with apixaban; only confidence intervals were calculated.

[e]Proximal and distal DVT that occurred between randomization and up to 10 to 13 days postoperatively, which corresponded to study days 12 to 15. A patient may have been included in both categories if they had both proximal and distal DVT.

eTable 3: Sensitivity analysis of the primary efficacy outcome after multiple imputation of non-valid information.[a]

Outcome	Postoperative osocimab				Preoperative osocimab		Enoxaparin (n = 102)	Apixaban (n = 100)
	0.3 mg/kg (n = 102)	0.6 mg/kg (n = 65)	1.2 mg/kg (n = 104)	1.8 mg/kg (n = 101)	0.3 mg/kg (n = 106)	1.8 mg/kg (n = 107)		
Primary outcome, % (90% CI)[b]	22.4 (14.9 to 29.9)	16.4 (8.1 to 24.8)	17.2 (10.5 to 24.0)	17.0 (10.3 to 23.6)	28.2 (20.1 to 36.3)	15.0 (8.1 to 21.9)	23.5 (16.0 to 31.0)	15.6 (9.1 to 22.1)
Mean number of imputed events	4.9	2.8	4.9	3.2	6.9	7.1	4.0	3.6
Risk difference osocimab vs enoxaparin, % (90% CI)	1.1 (–9.5 to 11.7)	7.1 (–4.1 to 18.3)	6.3 (–3.8 to 16.3)	6.5 (–3.5 to 16.5)	–4.7 (–15.7 to 6.3)	8.5 (–1.7 to 18.7)		
Risk difference osocimab vs apixaban, % (90% CI)	–6.9 (–16.8 to 3.1)	–0.9 (–11.4 to 9.7)	–1.7 (–11.0 to 7.6)	–1.4 (–10.7 to 7.9)	–12.6 (–22.9 to –2.4)	0.5 (–8.8 to 9.8)		

CI, confidence interval, DVT, deep vein thrombosis.

[a]This analysis was performed in all patients who received at least one dose of study medication.

[b]The primary efficacy outcome was the incidence of a composite of asymptomatic and symptomatic venous thromboembolism up to 10 to 13 days postoperatively, which corresponded to study days 12 to 15. None of the patients had pulmonary embolism and there were no deaths.

eTable 4: Secondary efficacy outcomes in the per-protocol population and in the modified intention-to-treat population.[a]

Per-protocol population								
Outcome	**Postoperative osocimab**				**Preoperative osocimab**		**Enoxaparin (n = 76)**	**Apixaban (n = 83)**
	0.3 mg/kg (n = 76)	**0.6 mg/kg (n = 51)**	**1.2 mg/kg (n = 79)**	**1.8 mg/kg (n = 78)**	**0.3 mg/kg (n = 77)**	**1.8 mg/kg (n = 80)**		
Secondary efficacy outcome, no. (% [90% CI])[b]	18 (23.7 [15.9 to 33.1])	8 (15.7 [8.1 to 26.5])	13 (16.5 [10.0 to 24.9])	14 (17.9 [11.2 to 26.6])	24 (31.2 [22.5 to 41.0])	9 (11.3 [6.0 to 18.8])	20 (26.3 [18.2 to 35.9])	13 (15.7 [9.5 to 23.7])
Risk difference, osocimab vs enoxaparin, % (90% CI)	2.6 (–8.9 to 14.2)	10.6 (–1.2 to 22.4)	9.9 (–0.9 to 20.6)	8.4 (–2.6 to 19.3)	–4.9 (–16.9 to 7.2)	15.1 (4.9 to 25.2)		
Risk difference, osocimab vs apixaban, % (90% CI)	–8.0 (–18.4 to 2.3)	–0.0 (–10.7 to 10.6)	–0.8 (–10.3 to 8.7)	–2.3 (–12.0 to 7.4)	–15.5 (–26.4 to –4.6)	4.4 (–4.4 to 13.2)		
Components of the secondary efficacy outcome[c]								
Asymptomatic DVT[d]	18 (23.7)	7 (13.7)	13 (16.5)	14 (17.9)	22 (28.6)	9 (11.3)	20 (26.3)	11 (13.3)
Symptomatic DVT[e]	1 (1.3)	1 (2.0)	1 (1.3)	2 (2.6)	2 (2.6)	0	1 (1.3)	1 (1.2)
Nonfatal pulmonary embolism	0	0	1 (1.3)	0	0	1 (1.3)	0	1 (1.2)
Modified intention-to-treat population								
Outcome	**Postoperative osocimab**				**Preoperative osocimab**		**Enoxaparin (n = 77)**	**Apixaban (n = 84)**
	0.3 mg/kg (n = 78)	**0.6 mg/kg (n = 53)**	**1.2 mg/kg (n = 81)**	**1.8 mg/kg (n = 81)**	**0.3 mg/kg (n = 77)**	**1.8 mg/kg (n = 80)**		
Secondary efficacy outcome, no. (% [90% CI])[b]	18 (23.1 [15.5 to 32.3])	8 (15.1 [7.7 to 25.6])	13 (16.0 [9.8 to 24.3])	14 (17.3 [10.8 to 25.7])	24 (31.2 [22.5 to 41.0])	9 (11.3 [6.0 to 18.8])	20 (26.0 [17.9 to 35.5])	13 (15.5 [9.4 to 23.5])
Risk difference, osocimab vs enoxaparin, % (90% CI)	2.9 (–8.5 to 14.3)	10.9 (–0.7 to 22.4)	9.9 (–0.7 to 20.5)	8.7 (–2.0 to 19.4)	–5.2 (–17.2 to 6.8)	14.7 (4.7 to 24.8)		
Risk difference, osocimab vs apixaban, % (90% CI)	–7.6 (–17.8 to 2.6)	0.4 (–10.0 to 10.8)	–0.6 (–9.9 to 8.8)	–1.8 (–11.3 to 7.7)	–15.7 (–26.5 to –4.9)	4.2 (–4.5 to 12.9)		
Components of the secondary efficacy outcome[c]								
Asymptomatic DVT[d]	18 (23.1)	7 (13.2)	13 (16.0)	14 (17.3)	22 (28.6)	9 (11.3)	20 (26.0)	11 (13.1)
Symptomatic DVT[e]	1 (1.3)	1 (1.9)	1 (1.2)	2 (2.5)	2 (2.6)	0	1 (1.3)	1 (1.2)
Nonfatal pulmonary embolism	0	0	1 (1.2)	0	0	1 (1.3)	0	1 (1.2)

CI, confidence interval; DVT, deep vein thrombosis.

[a]Efficacy outcomes were assessed in the per-protocol population, which comprised all patients who received at least one dose of study medication and who could be evaluated for the primary efficacy outcome and did not have an important deviation from the protocol with an impact on the primary efficacy variable, and in the modified intention-to-treat population, which comprised all patients who received at least one dose of study medication and who could be evaluated for the primary efficacy outcome.

[b]The secondary efficacy outcome was defined as a composite of the incidence of symptomatic DVT, nonfatal pulmonary embolism, fatal pulmonary embolism, or unexplained death for which pulmonary embolism could not be excluded up to day 150 (±7), or objectively confirmed asymptomatic DVT up to 10 to 13 days postoperatively, which corresponded to study days 12 to 15. Only positively adjudicated events that occurred up to day 150 (±7) were considered.

[c]The first event after randomization was considered and subsequent events of the same type are not shown. The number of component secondary efficacy outcome events does not necessarily add up to the total number of secondary efficacy outcome events. There were no cases of fatal pulmonary embolism or unexplained death for which pulmonary embolism could not be ruled out.
[d]Refers to events detected by mandatory bilateral venography.
[e]Three patients had symptomatic venous thromboembolism during the 150-day follow-up. Of these, one patient in the postoperative osocimab 1.2 mg/kg group had pulmonary embolism on day 70 (venography performed on day 10 had shown DVT); one patient given apixaban had pulmonary embolism on day 60 (venography performed on day 11 was normal); the remaining patient with symptomatic venous thromboembolism had received osocimab 0.3 mg/kg preoperatively and developed symptomatic DVT on day 100 (venography performed on day 15 was normal). One additional patient in the preoperative osocimab 1.8 mg/kg group had asymptomatic pulmonary embolism detected on day 15, after venography (performed 48 hours earlier) documented proximal DVT.

eTable 5: Bleeding and adverse events until study day 150 (±7).[a]

Outcome	Postoperative osocimab, mg/kg				Preoperative osocimab, mg/kg		Enoxaparin (n = 102)	Apixaban (n = 100)
	0.3 (n = 102)	0.6 (n = 65)	1.2 (n = 104)	1.8 (n = 101)	0.3 (n = 106)	1.8 (n = 107)		
Major or clinically relevant nonmajor bleeding, no. (% [90% CI])[b]	3 (2.9 [0.8 to 7.4])	0 (0.0 [0.0 to 4.5])	1 (1.0 [0.0 to 4.5])	3 (3.0 [0.8 to 7.5])	2 (1.9 [0.3 to 5.8])	6 (5.6 [3.1 to 11.8])	7 (6.9 [3.3 to 12.5])	2 (2.0 [0.4 to 6.2])
Risk difference, osocimab vs enoxaparin, % (90% CI)	3.9 (–1.0 to 8.9)	6.9 (2.7 to 11.0)	5.9 (1.5 to 10.3)	3.9 (–1.1 to 8.9)	5.0 (0.3 to 9.6)	0.4 (–5.3 to 6.1)		
Risk difference, osocimab vs apixaban, % (90% CI)	–0.9 (–4.5 to 2.6)	2.0 (–0.3 to 4.3)	1.0 (–1.8 to 3.8)	–1.0 (–4.6 to 2.6)	0.1 (–3.1 to 3.3)	–4.5 (–9.0 to 0.0)		
Major bleeding	0	0	0	0	0	2 (1.9)	0	0
Clinically relevant nonmajor bleeding[c]	3 (2.9)	0	1 (1.0)	3 (3.0)	2 (1.9)	4 (3.7)	7 (6.9)	2 (2.0)
Overall summary of adverse events, no. of patients (%)								
Any adverse event	74 (72.5)	48 (73.8)	78 (75.0)	69 (68.3)	77 (72.6)	88 (82.2)	78 (76.5)	68 (68.0)
Serious adverse event	9 (8.8)	4 (6.2)	11 (10.6)	7 (6.9)	5 (4.7)	9 (8.4)	12 (11.8)	5 (5.0)
Any adverse event resulting in permanent discontinuation of study drug	0	0	0	0	0	0	1 (1.0)	0
Decrease in platelets below the lower limit of normal, no. (%)	2 (2.0)	6 (9.2)	4 (3.8)	6 (5.9)	9 (8.5)	11 (10.3)	9 (8.8)	2 (2.0)
Hypersensitivity and infusion-related reactions, no. (%)	7 (6.9)	3 (4.6)	10 (9.6)	3 (3.0)	5 (4.7)	5 (4.7)	5 (4.9)	3 (3.0)

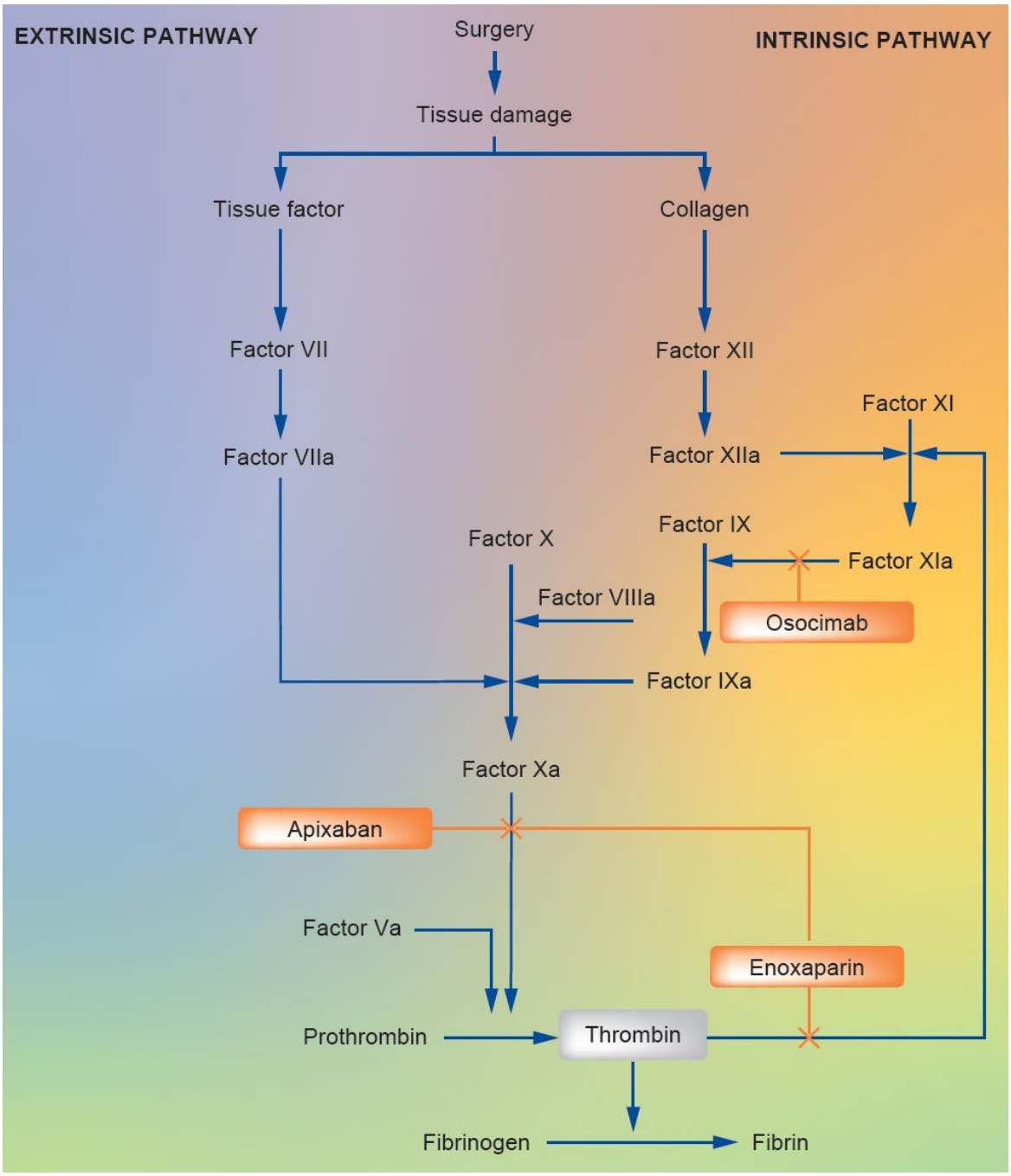
CI, confidence interval.

[a]Major or clinically relevant nonmajor bleeding events were assessed in all patients who received at least one dose of study medication.

[b]Major or clinically relevant nonmajor bleeding from randomization up to day 150 (±7).

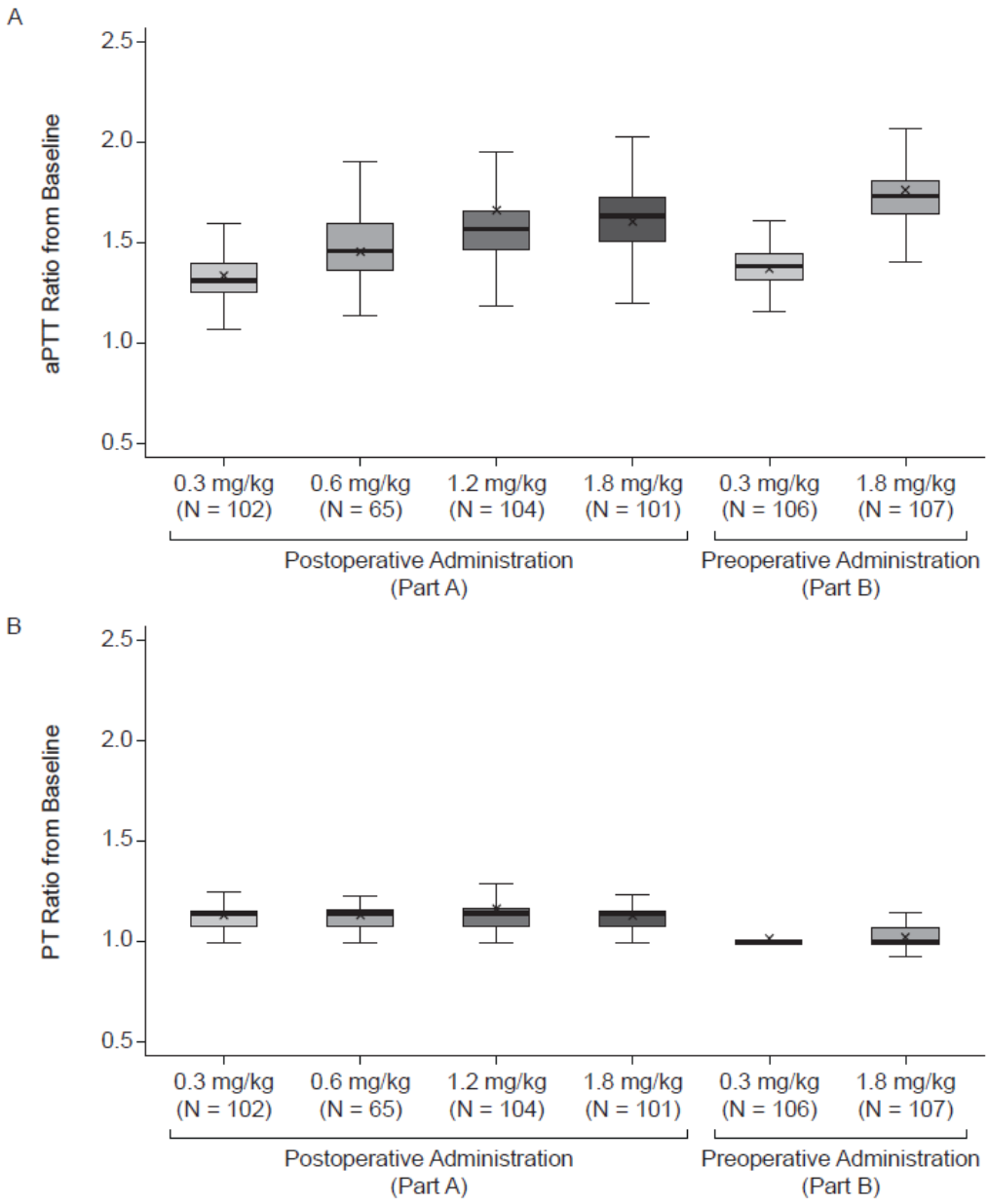
[c]Three patients had a clinically relevant nonmajor bleed during the follow-up period. One patient had nonmajor bleeding (hematuria in association with a kidney stone) 41 days after receiving osocimab 1.8 mg/kg preoperatively; no specific action was taken and bleeding resolved one day later. The second patient had a nonmajor upper gastrointestinal bleed associated with erosive gastritis 104 days after receiving osocimab 0.3 mg/kg postoperatively, which was treated with bismuth subcitrate and pantoprazole, among other medications, and resolved 5 days later. The third patient, who was in the enoxaparin group, had nonmajor lower gastrointestinal bleeding on day 15. The study drug had been withdrawn 14 days before the bleeding event owing to a serious acute coronary syndrome; however, at the time of the bleeding event, the patient was receiving enoxaparin and acetylsalicylic acid for the acute coronary syndrome. One additional patient had a major bleed (hemarthrosis) 23 days after receiving osocimab 1.8 mg/kg preoperatively; the patient was concurrently receiving therapeutic doses of enoxaparin for treatment of DVT.

eTable 6: Clinical description of infusion-related reactions.
In total, ten hypersensitivity and infusion-related reactions occurred in eight patients up to 3 days after the first exposure to study treatment. All of these were mild, and all patients recovered. In the group given osocimab 0.6 mg/kg postoperatively, one patient had an allergic skin reaction (facial dermatitis) that started approximately 9 hours after the end of the osocimab infusion and recovered spontaneously 4 days later. In the group given osocimab 1.2 mg/kg postoperatively, one patient had decreased blood pressure, and nausea and vomiting that started 10 minutes after the end of the osocimab infusion and resolved 50 minutes later. Intravenous saline was given to treat the decrease in blood pressure. Another patient had an allergic rash on the arms which started 3 days after osocimab treatment. The patient received intramuscular antazoline hydrochloride to treat the event, which resolved the next day. One patient suffered from nausea that started after completion of the osocimab infusion and resolved spontaneously within 15 minutes. Facial erythema was experienced by one patient approximately 2 hours after completion of the osocimab infusion and resolved spontaneously 4 hours later. In the group given osocimab 1.8 mg/kg postoperatively, two patients experienced an allergic rash. One had dermatitis around the surgical wound that started 2 days after completion of the osocimab infusion and resolved spontaneously 15 days later. The other event, a rash on both hands, occurred one day after osocimab treatment and lasted for 1 hour and 20 minutes. The patient received intravenous clemastine fumarate to treat the event. In the enoxaparin group, one patient experienced an allergic rash on the day after receiving the first dose. The patient was treated with methylprednisolone and dimethindene maleate intravenously, and the allergic rash resolved the next day.



eFigure 1: Effect of osocimab, enoxaparin, and apixaban on the coagulation system

Tissue damage during surgery exposes tissue factor and collagen. Tissue factor binds factor VIIa and triggers the extrinsic coagulation pathway, whereas collagen activates factor XII and initiates the intrinsic coagulation pathway. Thrombin can feed back and activate factor XI. Osocimab binds adjacent to the active site of factor XIa and prevents it from activating factor IX, thereby attenuating the intrinsic pathway of coagulation. Apixaban directly inhibits factor Xa, whereas enoxaparin catalyzes the inhibition of factor Xa and thrombin by antithrombin.



eFigure 2: Activated partial thromboplastin time and prothrombin time ratios measured within two hours after administration of osocimab.

Activated partial thromboplastin time (aPTT) ratios (A) and prothrombin time (PT) ratios (B) were calculated by dividing the aPTT and PT determined after osocimab administration by those determined at baseline.

In these box and whisker plots, the ends of the boxes are the 75th and 25th percentiles, while the horizontal lines within the boxes reflect the medians and the x symbols denote the means. The vertical lines extending from the boxes denote the highest and lowest values within 1.5 times the interquartile range. Values more than 1.5 times the interquartile range were outliers and are not shown.