Supplementary Appendix

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

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Outcome definitions

1. Venous thromboembolism (VTE)

1.1. Deep Vein Thrombosis (DVT) on the unilateral venography of the operated leg:

The diagnostic criteria for DVT will be a constant intraluminal filling defect of the same shape on two different images, or non-visualization of vein(s) in the presence of a sudden cut-off, or multiple radiological signs on one image (at least 2 of the 3) of non-filling with expansion of vessel (tramlining), abrupt cut-off and non-visualization of a (part) of a vein and/or diversion of flow. On a cine loop sequence, (recording a real time image) with limb rotation a filling defect or abrupt vein cut-off in continuous profile will be diagnostic of a DVT.

The result of the adjudication will be:

- No Clot
- Distal Clot
- Proximal Clot
- Distal and Proximal clot
- Not Evaluable Distal but No Proximal Clot
- Not Evaluable

1.2. Suspected DVT of the leg

Symptomatic DVT of the leg will be confirmed if there are typical symptoms of thrombosis associated with:

- Non-compressible vein segment on ultrasonography (US) of the deep veins of the leg, or
- An intraluminal filling defect and/or non-visualization of veins in the presence of a sudden cutoff on ascending venography or an intraluminal filling defect on computed tomography (CT) venography, or magnetic resonance imaging (MRI) venography.

If there was a previous DVT of the leg, the confirmation will require symptoms of DVT, and:

- An extension of an intraluminal filling defect, a new intraluminal filling defect, or an extension of non-visualization of veins in the presence of a sudden cut-off on venography, CT-scan, or MRI venography, or
- A non-compressible vein segment on ultrasonography where compression had been normal or a substantial increase ($\geq$ 4 mm) in the diameter of the thrombus during full compression (if previously non-compressible), or a different clot location compared with the clot location detected on venography.

1.3. Suspected Pulmonary Embolism (PE)

Symptomatic PE will be confirmed if there are typical symptoms of PE associated with:

- An intraluminal filling defect in (sub) segmental or more proximal branches on spiral CT, or CT pulmonary angiogram;
- An intraluminal filling defect or a sudden cutoff of vessels (more than 2.5 mm in diameter) on a catheter guided pulmonary angiogram;
- A large perfusion defect (~ 75% of a segment) with a normal ventilation result (high probability) on perfusion ventilation lung scan (PLS, VLS or V/Q scan); or
- An intermediate probability V/Q lung scan complemented by ultrasound or venographic evidence of DVT

Diagnosis of fatal PE is based on one or more of the following:

- Objective diagnostic testing
- Autopsy

- Death which cannot be attributed to a documented cause and for which PE cannot be completely ruled out

2. Bleeding events

Major Bleed
Since all patients will have had knee surgery, criteria for major bleeding in the surgical setting will be as described by Schulman et al. in JThromb Haemost 2010

- Fatal bleeding, and/or
- Bleeding that is symptomatic and occurs in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome, and/or
- Extra surgical site bleeding causing a fall in hemoglobin (Hb) level of 2.0 g/dL (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or packed red blood cells, with temporal association within 24 to 48 hours to the bleeding, and/or
- Surgical site bleeding that requires a second intervention (open, arthroscopic, endovascular), or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing resulting in prolonged hospitalization or a deep wound infection, and/or
- Surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability. There should be an associated fall in Hb-level of 2.0 g/dL) (1.24 mmol/L) or more, or transfusion, indicated by the bleeding, of at least 2 units of whole blood or packed red blood cells, with temporal association within 24 hours to the bleeding.

Clinically relevant nonmajor bleed
Overt bleeding not meeting the criteria for major bleeding, but that resulted in, for example, medical examination, intervention or had clinical consequences for a patient, will be classified as clinically relevant nonmajor (CRNM) bleeding.

Minor bleeding events

Overt bleeding events that do not fulfill the criteria for a major bleed or a clinically relevant nonmajor bleed will be classified as minor bleeds.

Non-overt bleeding events

Suspected bleeding events (e.g., decline in Hb without unusual blood loss during the knee surgery, or isolated microscopic hematuria) will be classified as “no bleeding event.”

3. Classification of cause of death

Death will be classified in below categories with respect to cause:
Cardiovascular (check one of the subcategories listed below)

- Myocardial Infarction
- Non-hemorrhagic Stroke
- Intracranial Hemorrhage
- Hemorrhage, not intracranial
- Congestive Heart Failure or Cardiogenic Shock
- Pulmonary Embolism
- Unknown but PE cannot be ruled out
- Other vascular (to be specified)

Non-Cardiovascular

- Accidental/Trauma
- Respiratory Failure
- Malignancy
- Suicide
- Liver Failure
- Renal Failure
- Infection/Sepsis
- Other non-vascular (to be specified)

Per Protocol analysis

Per protocol analysis set includes all mITT subjects with no key protocol deviations. Key protocol deviations are defined as follows:

- Developed withdrawal criteria but not withdrawn
- Randomized but did not satisfy key criteria
- Received a disallowed concomitant treatment
- Received study drug that is different from the treatment group randomized by the IWRS or an incorrect dose of study drug
- Was randomized but did not receive study drug

Table S1 Per Protocol Analysis: Efficacy Outcomes

Outcome	Milvexian Twice Daily				Milvexian Once Daily			Enoxaparin
	25 mg	50 mg	100 mg	200 mg	25 mg	50 mg	200 mg	40 mg
No. of patients evaluated	125	120	130	126	27	124	115	245
Primary efficacy outcome: total venous thromboembolism								
Any event – no. (%)	26 (21)	14 (12)	12 (9)	10 (8)	6 (22)	30 (24)	8 (7)	54 (22.0)
Relative risk milvexian vs. enoxaparin	0.94	0.52	0.42	0.37	0.87	1.15	0.32	NA
(95% confidence Interval)	(0.62-1.40)	(0.30-0.89)	(0.23-0.76)	(0.20-0.70)	(0.42-1.82)	(0.78-1.69)	(0.16-0.64)	NA
Components of the primary efficacy outcome – no. (%)								
Any death	0	0	0	0	0	0	0	1
Nonfatal pulmonary embolism	0	1	1	0	0	0	0	1
Symptomatic distal deep-vein thrombosis	0	0	1	0	0	2	0	0
Asymptomatic proximal deep-vein thrombosis	1	0	1	0	0	2	0	2
Asymptomatic distal deep-vein thrombosis	25	13	9	10	6	26	8	50
Extent of deep-vein thrombosis on venography – no.								
Confluent distal into proximal	1	0	1	0	0	2	0	1
Isolated proximal								
Large: ≥10 cm	0	0	0	0	0	0	0	0
Small: <10 cm	0	0	0	0	0	0	0	1
Isolated distal								
Extensive: ≥2 veins	9	5	1	2	4	9	1	20
Limited: <2 veins	16	8	9	8	2	18	7	30

Figure S1: Median hemoglobin values before and after surgery with milvexian and enoxaparin

The middle line indicates the median, the top and bottom of the box indicate the upper and lower limits, respectively, of the interquartile range.

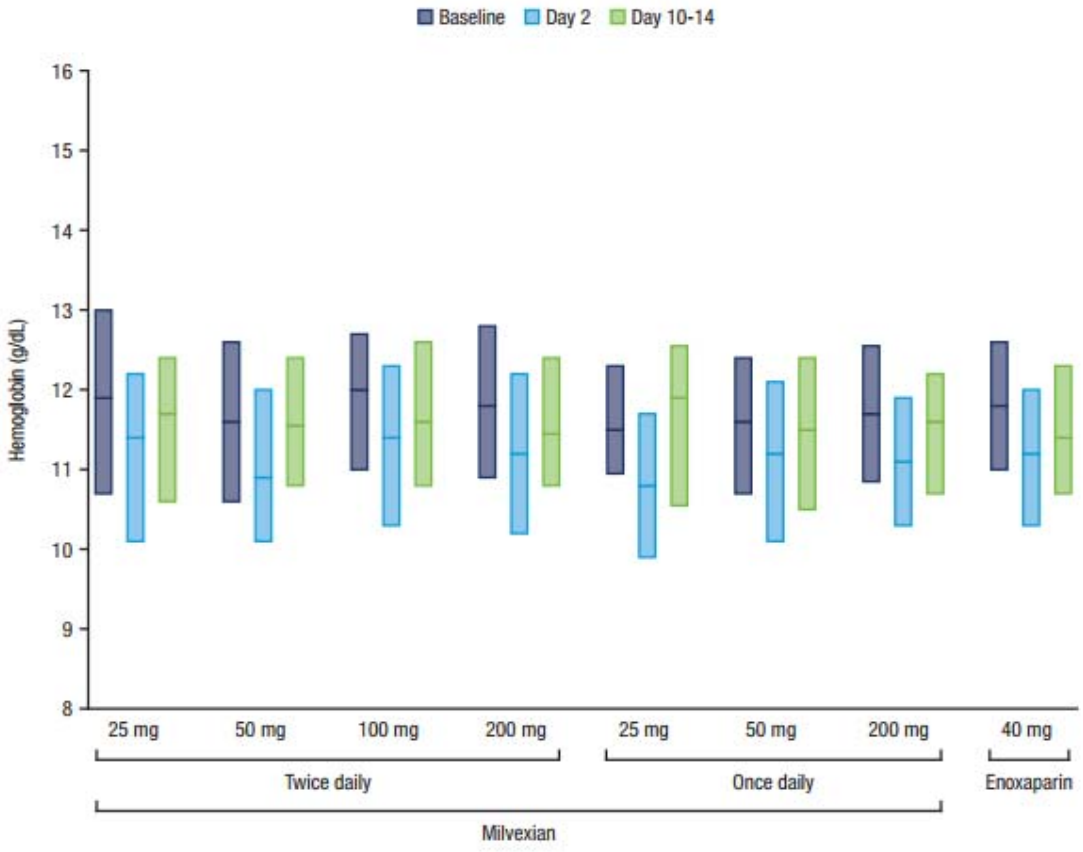

Figure S2 Mean prothrombin time ratios after surgery with milvexian and enoxaparin.

Prothrombin times measured after surgery on days 1, 4 and 10-14 were divided by baseline prothrombin times to calculate the prothrombin time ratios. The symbols indicate the means, whereas the bars above and below the symbols indicate the standard error of the mean.

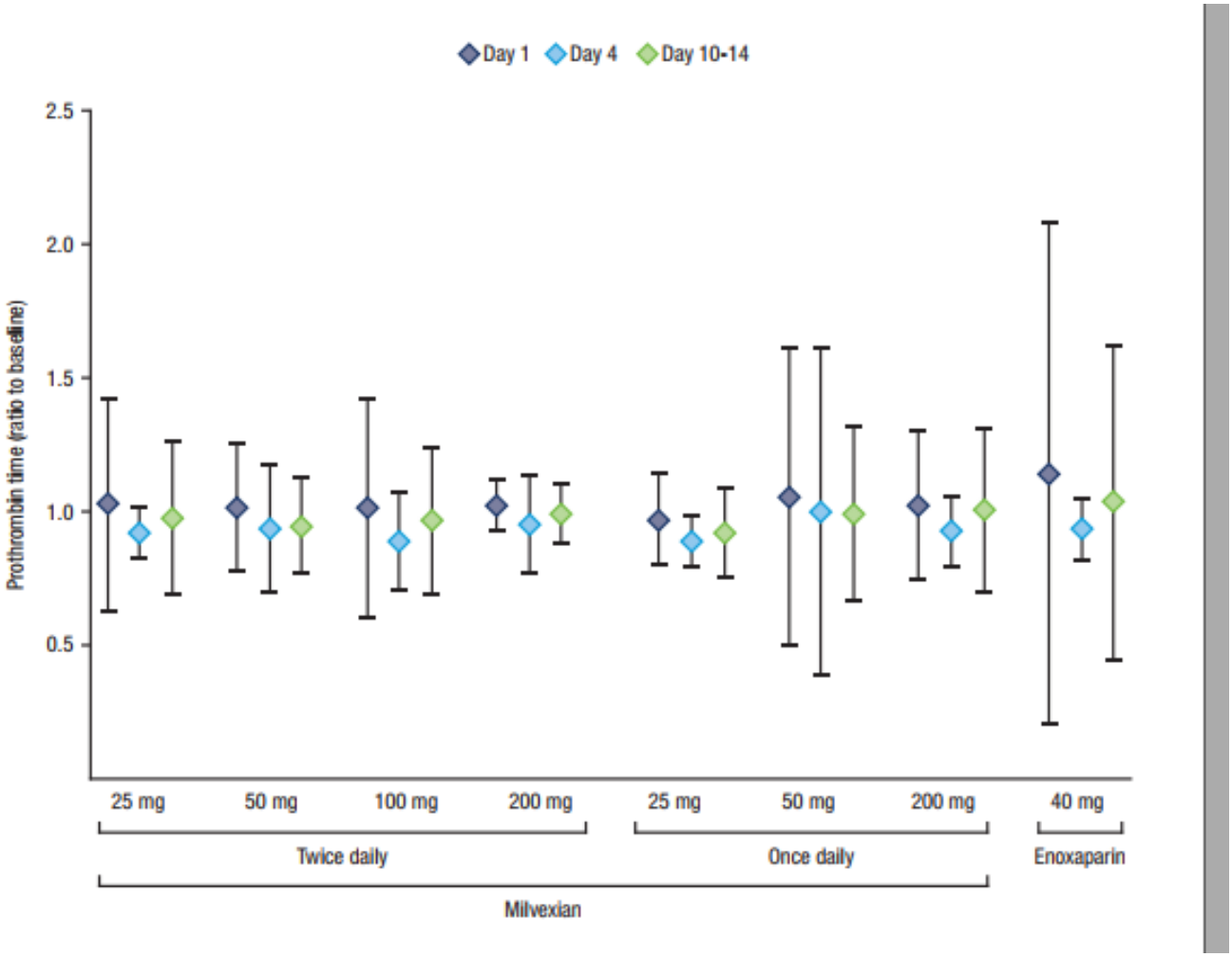

Table S2 Adverse Events by System Organ Class with milvexian and Enoxaparin

	Milvexian	Enoxaparin
Safety population – no.	923	296
Adverse events – no. (%)	358 (39)	113 (38)
System Organ Class		
Gastrointestinal	91 (10)	26 (9)
Investigations	76 (8)	25 (8)
Skin and subcutaneous tissue	55 (6)	16 (5)
Injury, poisoning and procedural complications	51 (6)	26 (9)
General disorders, administration site conditions	50 (5)	10 (3)
Vascular	37 (4)	5 (2)
Musculoskeletal and connective tissue	31 (3)	6 (2)
Psychiatric	29 (3)	4 (1)
Nervous system	28 (3)	8 (3)
Infections and infestations	20 (2)	12 (4)
Metabolism and nutrition	18 (2)	8 (3)
Blood and lymphatic system	17 (2)	5 (2)
Respiratory, thoracic and mediastinal	12 (1)	3 (1)
Renal and urinary	11 (1)	1 (0.3)
Hepatobiliary	8 (1)	2 (1)
Cardiac	6 (1)	2 (1)
Eye	6 (1)	0
Ear and labyrinth	4 (0.4)	0
Immune system	2 (0.2)	2 (1)
Surgical and medical procedures	1 (0.1)	0

Table S3 Serious adverse events with milvexian and enoxaparin

	Milvexian	Enoxaparin
Safety population - no.	923	296
No. with serious adverse event- no. (%)	22 (2)	11 (4)
Pulmonary embolism	2 (0.2)	1 (0.3)
Deep-vein thrombosis	7* (0.8)	0
Suspected pulmonary embolism	2† (0.2)	0
Suspected deep-vein thrombosis	0	1** (0.3)
Ischemic stroke	1 (0.1)	0
Femoral artery embolism	1 (0.1)	0
Coronavirus 2019 infection	0	2 (0.7)
Hyponatremia	0	2 (0.7)
Atrial fibrillation	1 (0.1)	0
Subdural hematoma	0	1‡ (0.3)
Hematoma	1¥ (0.1)	1¥ (0.3)
Suicide	0	1 0.3)
Periprosthetic fracture	1 (0.1)	0
Severe knee pain	1 (0.1)	0
Urosepsis	1 (0.1)	0
Wound infection	1 (0.1)	1 (0.3)
Respiratory failure	0	1 (0.3)
Anemia	2¶ (0.2)	0
Prolonged vomiting	1 (0.1)	0

*Asymptomatic deep-vein thrombosis was detected by venography; these were reported as serious adverse event because hospitalization was prolonged.

** Deep-vein thrombosis was suspected but was not confirmed by objective testing.

† Pulmonary embolism was suspected but was not confirmed by objective testing.

‡ Subdural hematoma was adjudicated as a major bleed.

¥ Hematomas were adjudicated as clinically relevant nonmajor bleeds..

¶ Anemia without evidence of overt bleeding.