



Clinical trial results: Causes and Prevention of Thromboembolic Disease in Nephrotic Syndrome Summary

EudraCT number	2019-001212-29
Trial protocol	DK
Global end of trial date	04 September 2024

Results information

Result version number	v1 (current)
This version publication date	23 April 2025
First version publication date	23 April 2025

Trial information

Trial identification

Sponsor protocol code	Prot-0824-2019
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04850378
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Department of Renal Medicine, Aarhus University Hospital, Denmark
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Sponsor organisation name	Department of Renal Medicine, Aarhus University Hospital, Denmark
Sponsor organisation address	Palle Juul-Jensens Boulevard 99, Aarhus N, Denmark, 8200
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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	01 April 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2024
Global end of trial reached?	Yes
Global end of trial date	04 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study aims to describe the biochemical coagulation profile and investigate the effect of dalteparin and apixaban on this profile in patients with nephrotic syndrom. More specifically, we will:

- 1 Identify abnormalities in the coagulation profile in nephrotic syndrom promoting a prothrombotic state.
- 2 Describe the effects of dalteparin on the biochemical coagulation profile in nephrotic syndrom.
- 3 Determine the levels of plasma apixaban and its effect on the biochemical coagulation profile in nephrotic syndrom compared with healthy controls.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and GCP guidelines. Ethics committee approval was obtained prior to trial initiation. All participants provided written informed consent. Subjects were covered by the national trial insurance scheme, and data were pseudonymised to ensure confidentiality.

Background therapy:

No background therapy was administered across all treatment arms.

Evidence for comparator:

Dalteparin is the standard thromboprophylactic treatment in nephrotic syndrome and was chosen as comparator to evaluate the pharmacodynamic profile of apixaban.

Actual start date of recruitment	01 April 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 57
Worldwide total number of subjects	57
EEA total number of subjects	57

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)	32
From 65 to 84 years	23
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Recruitment took place in Denmark from 1 April 2021 to May 1, 2025. Patients with nephrotic syndrome were recruited from both outpatient clinics and during hospital admission. Healthy volunteers were recruited via the national website for research recruitment, Forskning.nu.

Pre-assignment

Screening details:

Screening was done during outpatient visits and pathology conferences using recent p-albumin and ACR values (max one week old). Eligible patients were referred to investigator. Healthy volunteers were recruited via Forskning.nu.

Period 1

Period 1 title	Coagulation profile
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Blood samples were collected for coagulation profiling prior to any treatment. No investigational product was administered. Some participants ended study participation after this period, while others continued to the dalteparin period.

Arms

Arm title	Apixaban - Nephrotic syndrome
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Arm description:

This arm includes patients with nephrotic syndrome who underwent baseline blood sampling for coagulation profiling prior to any administration of apixaban. Apixaban is listed as the investigational product due to system requirements, but was not administered during this period.

Arm type	Experimental
Investigational medicinal product name	Apixaban
Investigational medicinal product code	B01AF02
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

No investigational medicinal product was administered during this period. Apixaban is included in the system due to technical requirements, but not given in this phase.

Number of subjects in period 1 ^[1]	Apixaban - Nephrotic syndrome
Started	47
Completed	47

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Healthy volunteers were included only for comparison during the apixaban intervention period, and not for baseline coagulation profiling. Therefore, the number of participants in the baseline period is lower than the total number enrolled.

Period 2

Period 2 title	Apixaban intervention
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Apixaban - Nephrotic syndrome

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Apixaban
Investigational medicinal product code	B01AF02
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg twice daily

Arm title	Apixaban - Healthy individuals
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Apixaban
Investigational medicinal product code	B01AF02
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg twice daily

Number of subjects in period 2^[2]	Apixaban - Nephrotic syndrome	Apixaban - Healthy individuals
Started	11	10
Completed	11	10

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total of 47 patients with nephrotic syndrome were included and completed the baseline period. Of these, 11 continued into the apixaban intervention period. In addition, 10 healthy individuals were included specifically for the apixaban intervention and were not part of the baseline period. Thus, 21 participants in total completed the apixaban intervention period, which explains the discrepancy in

subject numbers between the periods.

Baseline characteristics

Reporting groups

Reporting group title	Coagulation profile
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Reporting group description: -

Reporting group values	Coagulation profile	Total	
Number of subjects	47	47	
Age categorical			
Age			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	32	32	
From 65-84 years	13	13	
85 years and over	2	2	
Age continuous			
Mean age \pm SD at time of inclusion.			
Units: years			
arithmetic mean	47		
standard deviation	\pm 19	-	
Gender categorical			
Sex distribution at baseline.			
Units: Subjects			
Female	21	21	
Male	26	26	
Renal diagnosis			
Underlying renal diagnosis classified according to kidney biopsy or clinical evaluation at baseline.			
Units: Subjects			
Membranous nephropathy	15	15	
Minimal change disease	17	17	
Focal segmental glomerulosclerosis	4	4	
Proliferative glomerulonephritis	5	5	
Amyloidosis/Myeloma	4	4	
Other diagnosis	2	2	
Normal kidney	0	0	
Comorbidities			
Relevant comorbidities at baseline that may influence fluid balance or mimic nephrotic syndrome, including hypertension, heart failure, and liver failure			
Units: Subjects			
Hypertension	21	21	
Heart failure	1	1	
Liver failure	0	0	
No comorbidities	25	25	

eGFR			
Kidney function			
Units: Subjects			
eGFR > 90	15	15	
eGFR 60-90	20	20	
eGFR 30-59	12	12	
Plasma albumin			
Measured at baseline prior to any study treatment. Plasma albumin is a key clinical marker of nephrotic syndrome severity.			
Units: g/L			
arithmetic mean	22		
standard deviation	± 5	-	
Urine albumin creatinine ratio			
Measured at baseline prior to treatment. uACR is used to quantify proteinuria and assess disease severity in nephrotic syndrome.			
Units: mg/g			
median	4857		
inter-quartile range (Q1-Q3)	3611 to 6643	-	
D-dimer			
D-dimer measured at baseline to assess fibrin turnover and potential prothrombotic state.			
Units: mg/L			
median	0.93		
inter-quartile range (Q1-Q3)	0.56 to 1.30	-	
Fibrinogen			
Fibrinogen measured at baseline as a marker of coagulation activity and inflammation			
Units: µmol/L			
arithmetic mean	16.7		
standard deviation	± 4.4	-	
Median glycated hemoglobin			
Glycated hemoglobin (HbA1c) measured at baseline to assess long-term glucose regulation.			
Units: mmol/mol			
median	36		
inter-quartile range (Q1-Q3)	33 to 38	-	
Hemoglobin			
Hemoglobin measured at baseline as part of routine hematological assessment.			
Units: mmol/L			
arithmetic mean	8.8		
standard deviation	± 1.1	-	
White blood cells			
Leukocyte count measured at baseline as part of routine hematological assessment.			
Units: x 10 ⁹ /L			
arithmetic mean	8.3		
standard deviation	± 2.5	-	
Antithrombin			
Antithrombin activity measured at baseline to assess natural anticoagulant capacity			
Units: 10 ³ IU/L			
arithmetic mean	0.94		
standard deviation	± 0.20	-	
Protein C			
Protein C activity measured at baseline to evaluate natural anticoagulant function.			
Units: 10 ³ IU/L			
arithmetic mean	1.53		

standard deviation	± 0.30	-	
Protein S			
Protein S activity measured at baseline to assess natural anticoagulant status.			
Units: 10 ³ IU/L			
arithmetic mean	1.13		
standard deviation	± 0.22	-	
Coagulation factor VIII			
Factor VIII activity measured at baseline to assess procoagulant potential.			
Units: 10 ³ IU/L			
arithmetic mean	2.23		
standard deviation	± 0.58	-	
Coagulation factor X			
Factor X activity measured at baseline as part of the coagulation profile.			
Units: 10 ³ IU/L			
arithmetic mean	0.97		
standard deviation	± 0.19	-	
Platelet count			
Platelet count measured at baseline as part of routine hematological and coagulation assessment.			
Units: x 10 ⁹ /L			
arithmetic mean	296		
standard deviation	± 92	-	
TRAP			
Thrombin receptor-activating peptide (TRAP)-induced platelet aggregation measured at baseline to assess platelet function.			
Units: AU x min			
arithmetic mean	1231		
standard deviation	± 233	-	
ADP			
Adenosine diphosphate (ADP)-induced platelet aggregation measured at baseline to assess platelet function.			
Units: AU x min			
arithmetic mean	893		
standard deviation	± 251	-	
ASPI			
Arachidonic acid (ASPI)-induced platelet aggregation measured at baseline to assess platelet function.			
Units: AU x min			
arithmetic mean	1013		
standard deviation	± 215	-	
Thrombomodulin			
Soluble thrombomodulin measured at baseline as a marker of endothelial cell injury.			
Units: ng/mL			
arithmetic mean	30.2		
standard deviation	± 12.6	-	
Syndecan-1			
Syndecan-1 measured at baseline to assess shedding of the endothelial glycocalyx.			
Units: ng/mL			
median	91.9		
inter-quartile range (Q1-Q3)	58.5 to 152.3	-	
sE-selectin			
Soluble E-selectin measured at baseline as a marker of endothelial activation.			
Units: ng/mL			
arithmetic mean	39.7		

standard deviation	± 20.9	-	
Von Willebrand factor antigen			
von Willebrand factor measured at baseline as a marker of endothelial activation and prothrombotic potential.			
Units: 10 ³ IU/L			
arithmetic mean	3.0		
standard deviation	± 1.0	-	
ETP			
Endogenous thrombin potential (ETP) measured at baseline to assess thrombin-generating capacity ex vivo.			
Units: nM x min			
arithmetic mean	1398		
standard deviation	± 398	-	
F1+F2			
Prothrombin fragments 1+2 (F1+F2) measured at baseline as markers of in vivo thrombin generation.			
Units: pmol/L			
arithmetic mean	509		
standard deviation	± 269	-	
TAT complex			
Thrombin-antithrombin (TAT) complexes measured at baseline to assess in vivo thrombin generation and coagulation activation.			
Units: µmol/l			
arithmetic mean	3.5		
standard deviation	± 1.0	-	
50% clot lysis			
Time to 50% clot lysis measured at baseline to evaluate fibrinolytic capacity.			
Units: s.			
arithmetic mean	1281		
standard deviation	± 533	-	
Thromboxane B			
Thromboxane B (TXB) measured at baseline as a marker of platelet activation and thromboxane synthesis.			
Units: ng/L			
arithmetic mean	282		
standard deviation	± 159	-	

Subject analysis sets

Subject analysis set title	Apixaban - Nephrotic syndrome
Subject analysis set type	Full analysis
Subject analysis set description:	
Plasma apixaban and its effect on the coagulation profile in patients with nephrotic syndrome	
Subject analysis set title	Apixaban - Healthy individuals
Subject analysis set type	Full analysis
Subject analysis set description:	
Plasma apixaban and its effect on the coagulation profile in patients with nephrotic syndrome	

Reporting group values	Apixaban - Nephrotic syndrome	Apixaban - Healthy individuals	
Number of subjects	11	10	
Age categorical			
Age			
Units: Subjects			

In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	11	10	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Mean age \pm SD at time of inclusion.			
Units: years			
arithmetic mean	51	36	
standard deviation	\pm 19	\pm 19	
Gender categorical			
Sex distribution at baseline.			
Units: Subjects			
Female	4	6	
Male	7	4	
Renal diagnosis			
Underlying renal diagnosis classified according to kidney biopsy or clinical evaluation at baseline.			
Units: Subjects			
Membranous nephropathy	5	0	
Minimal change disease	4	0	
Focal segmental glomerulosclerosis	2	0	
Proliferative glomerulonephritis	0	0	
Amyloidosis/Myeloma	0	0	
Other diagnosis	0	0	
Normal kidney	0	10	
Comorbidities			
Relevant comorbidities at baseline that may influence fluid balance or mimic nephrotic syndrome, including hypertension, heart failure, and liver failure			
Units: Subjects			
Hypertension	5	0	
Heart failure	1	0	
Liver failure	0	0	
No comorbidities	5	10	
eGFR			
Kidney function			
Units: Subjects			
eGFR > 90	4	8	
eGFR 60-90	5	2	
eGFR 30-59	2	0	
Plasma albumin			
Measured at baseline prior to any study treatment. Plasma albumin is a key clinical marker of nephrotic syndrome severity.			
Units: g/L			
arithmetic mean	19	39	
standard deviation	\pm 3	\pm 3	
Urine albumin creatinine ratio			
Measured at baseline prior to treatment. uACR is used to quantify proteinuria and assess disease			

severity in nephrotic syndrome.			
Units: mg/g			
median	5029	6.5	
inter-quartile range (Q1-Q3)	3919 to 8115	2 to 11	
D-dimer			
D-dimer measured at baseline to assess fibrin turnover and potential prothrombotic state.			
Units: mg/L			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 0	0 to 0	
Fibrinogen			
Fibrinogen measured at baseline as a marker of coagulation activity and inflammation			
Units: µmol/L			
arithmetic mean	0	0	
standard deviation	± 0	± 0	
Median glycated hemoglobin			
Glycated hemoglobin (HbA1c) measured at baseline to assess long-term glucose regulation.			
Units: mmol/mol			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 0	0 to 0	
Hemoglobin			
Hemoglobin measured at baseline as part of routine hematological assessment.			
Units: mmol/L			
arithmetic mean	8.8	8.5	
standard deviation	± 0.9	± 1.1	
White blood cells			
Leukocyte count measured at baseline as part of routine hematological assessment.			
Units: x 10 ⁹ /L			
arithmetic mean	8.0	5.9	
standard deviation	± 0.9	± 1.0	
Antithrombin			
Antithrombin activity measured at baseline to assess natural anticoagulant capacity			
Units: 10 ³ IU/L			
arithmetic mean	0	0	
standard deviation	± 0	± 0	
Protein C			
Protein C activity measured at baseline to evaluate natural anticoagulant function.			
Units: 10 ³ IU/L			
arithmetic mean	1.53	1.13	
standard deviation	± 0.17	± 0.14	
Protein S			
Protein S activity measured at baseline to assess natural anticoagulant status.			
Units: 10 ³ IU/L			
arithmetic mean	1.12	0.92	
standard deviation	± 0.16	± 0.16	
Coagulation factor VIII			
Factor VIII activity measured at baseline to assess procoagulant potential.			
Units: 10 ³ IU/L			
arithmetic mean	0	0	
standard deviation	± 0	± 0	
Coagulation factor X			
Factor X activity measured at baseline as part of the coagulation profile.			
Units: 10 ³ IU/L			

arithmetic mean	0	0	
standard deviation	± 0	± 0	
Platelet count			
Platelet count measured at baseline as part of routine hematological and coagulation assessment.			
Units: x 10 ⁹ /L			
arithmetic mean	314	276	
standard deviation	± 101	± 86	
TRAP			
Thrombin receptor-activating peptide (TRAP)-induced platelet aggregation measured at baseline to assess platelet function.			
Units: AU x min			
arithmetic mean	0	0	
standard deviation	± 0	± 0	
ADP			
Adenosine diphosphate (ADP)-induced platelet aggregation measured at baseline to assess platelet function.			
Units: AU x min			
arithmetic mean	0	0	
standard deviation	± 0	± 0	
ASPI			
Arachidonic acid (ASPI)-induced platelet aggregation measured at baseline to assess platelet function.			
Units: AU x min			
arithmetic mean	0	0	
standard deviation	± 0	± 0	
Thrombomodulin			
Soluble thrombomodulin measured at baseline as a marker of endothelial cell injury.			
Units: ng/mL			
arithmetic mean	0	0	
standard deviation	± 0	± 0	
Syndecan-1			
Syndecan-1 measured at baseline to assess shedding of the endothelial glycocalyx.			
Units: ng/mL			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 0	0 to 0	
sE-selectin			
Soluble E-selectin measured at baseline as a marker of endothelial activation.			
Units: ng/mL			
arithmetic mean	0	0	
standard deviation	± 0	± 0	
Von Willebrand factor antigen			
von Willebrand factor measured at baseline as a marker of endothelial activation and prothrombotic potential.			
Units: 10 ³ IU/L			
arithmetic mean	3.1	1.4	
standard deviation	± 1.2	± 0.03	
ETP			
Endogenous thrombin potential (ETP) measured at baseline to assess thrombin-generating capacity ex vivo.			
Units: nM x min			
arithmetic mean	1435	1190	
standard deviation	± 453	± 340	
F1+F2			
Prothrombin fragments 1+2 (F1+F2) measured at baseline as markers of in vivo thrombin generation.			

Units: pmol/L			
arithmetic mean	420	193	
standard deviation	± 179	± 71	
TAT complex			
Thrombin-antithrombin (TAT) complexes measured at baseline to assess in vivo thrombin generation and coagulation activation.			
Units: µmol/l			
arithmetic mean	3.3	3.0	
standard deviation	± 1.0	± 1.9	
50% clot lysis			
Time to 50% clot lysis measured at baseline to evaluate fibrinolytic capacity.			
Units: s.			
arithmetic mean	1180	751	
standard deviation	± 368	± 232	
Thromboxane B			
Thromboxane B (TXB) measured at baseline as a marker of platelet activation and thromboxane synthesis.			
Units: ng/L			
arithmetic mean	0	0	
standard deviation	± 0	± 0	

End points

End points reporting groups

Reporting group title	Apixaban - Nephrotic syndrome
Reporting group description: This arm includes patients with nephrotic syndrome who underwent baseline blood sampling for coagulation profiling prior to any administration of apixaban. Apixaban is listed as the investigational product due to system requirements, but was not administered during this period.	
Reporting group title	Apixaban - Nephrotic syndrome
Reporting group description: -	
Reporting group title	Apixaban - Healthy individuals
Reporting group description: -	
Subject analysis set title	Apixaban - Nephrotic syndrome
Subject analysis set type	Full analysis
Subject analysis set description: Plasma apixaban and its effect on the coagulation profile in patients with nephrotic syndrome	
Subject analysis set title	Apixaban - Healthy individuals
Subject analysis set type	Full analysis
Subject analysis set description: Plasma apixaban and its effect on the coagulation profile in patients with nephrotic syndrome	

Primary: Plasma apixaban concentration at steady state

End point title	Plasma apixaban concentration at steady state
End point description: Plasma apixaban concentrations were measured at steady state (Day 4–7) to evaluate drug exposure in patients with nephrotic syndrome and healthy volunteers after 5 mg twice daily dosing.	
End point type	Primary
End point timeframe: Day 4–7 after start of apixaban treatment (steady state).	

End point values	Apixaban - Nephrotic syndrome	Apixaban - Healthy individuals		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: µg/L				
arithmetic mean (confidence interval 95%)	35 (28 to 43)	51 (39 to 64)		

Statistical analyses

Statistical analysis title	Unpaired t-test
Comparison groups	Apixaban - Healthy individuals v Apixaban - Nephrotic syndrome

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.02
Method	t-test, 2-sided

Secondary: ETP at steady state

End point title	ETP at steady state
End point description: Endogenous thrombin potential (ETP) measured at steady state (Day 4–7) to assess thrombin-generating capacity following apixaban treatment in nephrotic patients and healthy individuals.	
End point type	Secondary
End point timeframe: Day 4–7 (steady state)	

End point values	Apixaban - Nephrotic syndrome	Apixaban - Healthy individuals		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: mmol x min				
arithmetic mean (confidence interval 95%)	1096 (868 to 1324)	910 (713 to 1107)		

Statistical analyses

Statistical analysis title	Unpaired t-test
Comparison groups	Apixaban - Nephrotic syndrome v Apixaban - Healthy individuals
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.18
Method	t-test, 2-sided

Secondary: F1+F2 at steady state

End point title	F1+F2 at steady state
End point description: rothrombin fragments 1+2 (F1+F2) measured at steady state (Day 4–7) as markers of in vivo thrombin generation and coagulation activation in nephrotic patients and healthy individuals.	
End point type	Secondary
End point timeframe: Day 4–7 (steady state)	

End point values	Apixaban - Nephrotic syndrome	Apixaban - Healthy individuals		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: pmol				
arithmetic mean (confidence interval 95%)	223 (175 to 268)	145 (98 to 191)		

Statistical analyses

Statistical analysis title	Unpaired t-test
Comparison groups	Apixaban - Nephrotic syndrome v Apixaban - Healthy individuals
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.02
Method	t-test, 2-sided

Secondary: TAT at steady state

End point title	TAT at steady state
End point description: Thrombin-antithrombin (TAT) complexes measured at steady state (Day 4–7) as markers of in vivo thrombin generation and coagulation activation in nephrotic patients and healthy individuals.	
End point type	Secondary
End point timeframe: Day 4–7 (steady state)	

End point values	Apixaban - Nephrotic syndrome	Apixaban - Healthy individuals		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: µmol/L				
arithmetic mean (confidence interval 95%)	2.2 (1.5 to 29)	2.2 (1.1 to 3.0)		

Statistical analyses

Statistical analysis title	Unpaired t-test
Comparison groups	Apixaban - Nephrotic syndrome v Apixaban - Healthy individuals
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.95
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From treatment initiation (Day 1) to 7 days after the end of treatment (Day 7).

Adverse event reporting additional description:

Adverse events were recorded from treatment initiation (Day 1) through 7 days after the end of treatment (Day 7) for both Dalteparin and Apixaban. Events were classified and graded according to standard clinical guidelines. Follow-up included assessment of any ongoing or new adverse events at Day 7 after treatment cessation.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Nephrotic patients
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Reporting group description: -

Reporting group title	Healthy individuals
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Reporting group description: -

Serious adverse events	Nephrotic patients	Healthy individuals	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Nephrotic patients	Healthy individuals	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 11 (18.18%)	1 / 10 (10.00%)	
Gastrointestinal disorders			
Hemorrhoidal bleeding	Additional description: One patient with nephrotic syndrome reported well-known intermittent hemorrhoidal bleeding, which similarly occurred under apixaban treatment.		
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Heavier menstrual bleeding	Additional description: One healthy individual reported slightly heavier menstrual bleeding while on apixaban.		

subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 10 (10.00%) 1	
Skin and subcutaneous tissue disorders			
Epistaxis	Additional description: One patient with nephrotic syndrome experienced known intermittent epistaxis, which also occurred during apixaban treatment.		
subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 January 2021	1) Increased participant number in sub-study 2 from 30 to 50. 2) Treatment duration for both sub-study 2 and 3 extended from 4 days to 4-7 days for Fragmin and Eliquis. 3) Participants will keep a medication diary. 4) Additional blood samples for endothelial function and hyperlipidemia analysis. 5) Optional kidney biopsy for up to 10 participants in sub-study 1 (Jan 10, 2021). 6) Optional transjugular liver biopsy for up to 10 participants in sub-study 1.
19 March 2021	1) Inclusion criterion for plasma albumin changed in all three sub-studies: Sub-study 1: Plasma albumin increased from <20 g/L to <30 g/L Sub-studies 2 and 3: Plasma albumin increased from <20 g/L to <25 g/L 2) Participant number in sub-study 1 increased to 60. Substudy 1: coagulation profile, substudy 2: dalteaprin, substudy 3: apixaban
08 August 2021	1) Inclusion criteria changed for all sub-studies and control groups: Age increased from 18-80 years to > 18 years eGFR increased from > 49 to > 30 ml/min/1.73m ² Well-regulated diabetes with HbA1c < 65 mmol/mol Exclusion criteria updated: Diabetes excluded from all sub-studies and control groups New exclusion criterion for AFIB patients: If infection suspected, CRP must be < 30 g/L Study medication dosage updated: Apixaban can be administered as 5 mg x 2 or 2.5 mg x 2 depending on age, weight, and renal function Follow-up via journal audit within 5 years: Added follow-up via journal audit within 5 years to the protocol and participant information.
21 December 2021	1) Two new sites added: Department of Medicine, Regional Hospital Gødstrup, Hospitalsparken 15, DK-7400 Herning Department of Medicine, Regional Hospital Viborg, Heibergs Alle 5A, DK-8800 Viborg

29 April 2022	<p>1) The control group in sub-study 3 is changed from 10 patients with atrial fibrillation (no patients enrolled yet) to 10 healthy volunteers.</p> <p>2) Justification for change: This change is requested because atrial fibrillation patients were more comorbid than expected, which could have a significant impact on coagulation. Therefore, it was concluded that the comparison group would not provide sufficient data, and healthy volunteers are now sought to achieve more valid comparison results.</p>
11 July 2022	<p>1) Inclusion criteria for the disease group in the apixaban group are expanded to include not only patients with membranous nephropathy, but also patients with Minimal Change Disease and Focal Segmental Glomerulosclerosis.</p> <p>2) Justification for change: The inclusion criteria are expanded to ensure inclusion of more patients, and by including multiple glomerular diseases, a broader understanding of how Eliquis works in patients with nephrotic syndrome can be achieved.</p>

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.

<p>The study had a small sample size, which limits the statistical power and generalizability of the results. The study only followed patients for a short period (4-7 days), so long-term effects of treatment are unknown.</p>
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Notes: