



## Clinical trial results:

### Direct thrombin inhibitors versus low molecular weight heparins as thromboprophylaxis in Staphylococcus aureus bacteraemia. A prospective randomized controlled academic single-centre feasibility study

#### Summary

EudraCT number	2012-004863-29
Trial protocol	BE
Global end of trial date	08 August 2016

#### Results information

Result version number	v1 (current)
This version publication date	28 February 2021
First version publication date	28 February 2021

#### Trial information

##### Trial identification

Sponsor protocol code	1M
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##### Additional study identifiers

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

Notes:

##### Sponsors

Sponsor organisation name	University Hospitals Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Peter Verhamme, university hospitals Leuven (Gasthuisberg), +32 16341463,
Scientific contact	Peter Verhamme, university hospitals Leuven (Gasthuisberg), +32 16341463,

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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	08 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 August 2016
Global end of trial reached?	Yes
Global end of trial date	08 August 2016
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

Feasibility and safety of direct thrombin inhibitors (dabigatran or argatroban) versus LMWH (clexane) in patients with staphylococcus aureus bacteraemia. Effect on coagulation parameters.

Protection of trial subjects:

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Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Scientific research
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Belgium: 94
Worldwide total number of subjects	94
EEA total number of subjects	94

Notes:

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**Subjects enrolled per age group**

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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)	42
From 65 to 84 years	52
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

All patients aged 18 years and older with blood cultures growing *S. aureus* and with symptoms or signs of infection, for whom prophylaxis of venous thromboembolism was indicated, were eligible for the study. Between March 2013 and July 2016, 303 patients were eligible.

### Pre-assignment

Screening details:

Regarding feasibility, 209 of the 303 patients were excluded from the trial. The main reasons for exclusion were kidney or liver failure, planned surgery, recent bleeding, thrombocytopenia and contraindications related to study drug administration. The remaining 94 patients were randomized 1:1.

### Period 1

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

Blinding implementation details:

Due to different routes of administration of dabigatran, argatroban and LMWH, the study physician and data collection team, nor the patient were blinded for the intervention during the trial. The technicians who performed laboratory analyses, the investigators who performed and interpreted the medical imaging and the investigators performing bleeding severity adjudication were blinded to treatment group.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Direct thrombin inhibitor

Arm description:

Dabigatran or argatroban

Arm type	Experimental
Investigational medicinal product name	dabigatran
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

110 mg BID

Investigational medicinal product name	argatroban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

argatroban according to aPTT 1.5-2ULN

<b>Arm title</b>	Enoxaparin
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Arm description:

enoxaparin 40 mg OD SC

Arm type	Active comparator
Investigational medicinal product name	enoxaparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

enoxaparin 40 mg

<b>Number of subjects in period 1</b>	Direct thrombin inhibitor	Enoxaparin
Started	47	47
Completed	47	47

## Baseline characteristics

### Reporting groups

Reporting group title	Direct thrombin inhibitor
Reporting group description: Dabigatran or argatroban	
Reporting group title	Enoxaparin
Reporting group description: enoxaparin 40 mg OD SC	

Reporting group values	Direct thrombin inhibitor	Enoxaparin	Total
Number of subjects	47	47	94
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age of all patients included in the full analysis set			
Units: years			
median	64	63	
standard deviation	± 15	± 18	-
Gender categorical			
Gender of all patients included in the full-analysis set			
Units: Subjects			
Female	7	20	27
Male	40	27	67

## End points

### End points reporting groups

Reporting group title	Direct thrombin inhibitor
Reporting group description: Dabigatran or argatroban	
Reporting group title	Enoxaparin
Reporting group description: enoxaparin 40 mg OD SC	

### Primary: Bleeding

End point title	Bleeding
End point description: Bleeding	
End point type	Primary
End point timeframe: During study drug treatment and until 3 days after the end of the study period	

End point values	Direct thrombin inhibitor	Enoxaparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: whole				
Major bleeding	1	1		
Clinically relevant non major bleeding	4	4		
Gastro intestinal tract	2	0		
Respiratory tract	2	0		
Urogenital tract	0	2		
post intervention	0	2		
Minor bleeding	4	6		

### Statistical analyses

Statistical analysis title	intention to treat
Statistical analysis description: The study was not powered to detect significant differences in the Clinical outcomes due to the small study population. Statistical analysis was done in an intention to treat model (retaining all participants in their originally assigned group), as well as per protocol (defined as patients that received at least 80% of sheduled doses of DTI from randomization to day 4, compared with control patients). We uses GraphPad Prism and utilized appropriate tests to compare variables between groups.	
Comparison groups	Direct thrombin inhibitor v Enoxaparin

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	= 0.45
Method	GraphPad Prism

Notes:

[1] - An intention to treat model. A preliminary power calculation was based on a differential evolution of D dimers in DTI treated versus control patients. We hypothesized that DTIs would result in a more rapid resolution of coagulation activation in S Aureus bacteraemia. With an estimated D dimer decline of 1.000 ng/mL in the DTI group versus 500 ng/mL in the control group, a sample size 2X50 patients has 80% power to detect such difference.

## Secondary: hospital stay

End point title	hospital stay
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End point description:

End point type	Secondary
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End point timeframe:

whole study

End point values	Direct thrombin inhibitor	Enoxaparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: whole	19	16		

## Statistical analyses

Statistical analysis title	intention to treat
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Statistical analysis description:

The study was not powered to detect significant differences in the Clinical outcomes due to the small study population. Statistical analysis was done in an intention to treat model (retaining all participants in their originally assigned group), as well as per protocol (defined as patients that received at least 80% of scheduled doses of DTI from randomization to day 4, compared with control patients). We used GraphPad Prism and utilized appropriate tests to compare variables between groups.

Comparison groups	Direct thrombin inhibitor v Enoxaparin
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other <sup>[2]</sup>
P-value	= 0.27
Method	GraphPad Prism

Notes:

[2] - An intention to treat model. A preliminary power calculation was based on a differential evolution of D dimers in DTI treated versus control patients. We hypothesized that DTIs would result in a more rapid resolution of coagulation activation in S Aureus bacteraemia. With an estimated D dimer decline of 1.000 ng/mL in the DTI group versus 500 ng/mL in the control group, a sample size 2X50 patients has 80% power to detect such difference.

## Secondary: 90 day mortality

End point title	90 day mortality
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End point description:

End point type	Secondary
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End point timeframe:  
whole study

End point values	Direct thrombin inhibitor	Enoxaparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: whole	10	9		

## Statistical analyses

Statistical analysis title	intention to treat
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Statistical analysis description:

The study was not powered to detect significant differences in the Clinical outcomes due to the small study population. Statistical analysis was done in an intention to treat model (retaining all participants in their originally assigned group), as well as per protocol (defined as patients that received at least 80% of scheduled doses of DTI from randomization to day 4, compared with control patients). We used GraphPad Prism and utilized appropriate tests to compare variables between groups.

Comparison groups	Direct thrombin inhibitor v Enoxaparin
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
P-value	> 0.99
Method	GraphPad Prism

Notes:

[3] - An intention to treat model. A preliminary power calculation was based on a differential evolution of D dimers in DTI treated versus control patients. We hypothesized that DTIs would result in a more rapid resolution of coagulation activation in S Aureus bacteraemia. With an estimated D dimer decline of 1.000 ng/mL in the DTI group versus 500 ng/mL in the control group, a sample size 2X50 patients has 80% power to detect such difference.

## Secondary: Thrombosis

End point title	Thrombosis
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End point description:  
Total Thrombosis

End point type	Secondary
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End point timeframe:  
whole study



End point values	Direct thrombin inhibitor	Enoxaparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: whole				
Arterial thromboembolism	1	1		
Superficial venous thrombophlebitis	4	5		
Deep vein thrombosis	2	1		

## Statistical analyses

Statistical analysis title	intention to treat
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Statistical analysis description:

The study was not powered to detect significant differences in the Clinical outcomes due to the small study population. Statistical analysis was done in an intention to treat model (retaining all participants in their originally assigned group), as well as per protocol (defined as patients that received at least 80% of scheduled doses of DTI from randomization to day 4, compared with control patients). We used GraphPad Prism and utilized appropriate tests to compare variables between groups.

Comparison groups	Direct thrombin inhibitor v Enoxaparin
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other <sup>[4]</sup>
P-value	> 0.99
Method	GraphPad Prism

Notes:

[4] - An intention to treat model. A preliminary power calculation was based on a differential evolution of D dimers in DTI treated versus control patients. We hypothesized that DTIs would result in a more rapid resolution of coagulation activation in S Aureus bacteraemia. With an estimated D dimer decline of 1.000 ng/mL in the DTI group versus 500 ng/mL in the control group, a sample size 2X50 patients has 80% power to detect such difference.

## Other pre-specified: Defervescence

End point title	Defervescence
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End point description:

End point type	Other pre-specified
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End point timeframe:

whole study

End point values	Direct thrombin inhibitor	Enoxaparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: whole	26	12		

## Statistical analyses

<b>Statistical analysis title</b>	intention to treat
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### Statistical analysis description:

The study was not powered to detect significant differences in the Clinical outcomes due to the small study population. Statistical analysis was done in an intention to treat model (retaining all participants in their originally assigned group), as well as per protocol (defined as patients that received at least 80% of sheduled doses of DTI from randomization to day 4, compared with control patients). We uses GraphPad Prism and utilized appropriate tests to compare variables between groups.

Comparison groups	Direct thrombin inhibitor v Enoxaparin
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other <sup>[5]</sup>
P-value	= 0.3
Method	GraphPad Prism

### Notes:

[5] - An intention to treat model. A preliminary power calculation was based on a differential evolution of D dimers in DTI treated versus control patients. We hypothesized that DTIs would result in a more rapid resolution of coagulation activation in S Aureus bacteraemia. With an estimated D dimer decline of 1.000 ng/mL in the DTI group versus 500 ng/mL in the control group, a sample size 2X50 patients has 80% power to detect such difference.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

3 months after inclusion

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	ISTH major bleeding
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Dictionary version	0
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### Reporting groups

Reporting group title	Direct thrombin inhibitor
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Reporting group description: -

Reporting group title	Enoxaparin
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Reporting group description: -

Serious adverse events	Direct thrombin inhibitor	Enoxaparin	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	
number of deaths (all causes)	10	9	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Direct thrombin inhibitor	Enoxaparin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 47 (14.89%)	8 / 47 (17.02%)	
Infections and infestations			
relapse infection	Additional description: Relapse of S. Aureus bacteraemia		
subjects affected / exposed	2 / 47 (4.26%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
metastatic infection	Additional description: Metastatic infection on PET/CT. Not all patients received planned PET/CT: DTI Group: 30 patients received PET/CT (2/30) Control group: 27 patients received PET/CT (6/27)		
subjects affected / exposed	2 / 47 (4.26%)	6 / 47 (12.77%)	
occurrences (all)	2	6	
infective endocarditis			
subjects affected / exposed	3 / 47 (6.38%)	2 / 47 (4.26%)	
occurrences (all)	3	2	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.

The feasibility of the broad application of DTI in septic patients is limited by their anticoagulant action, hence explaining the large proportion of excluded patients (with bleeding risk) and the non-negligible number of bleeding events.
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Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29614521>