



Clinical trial results:

Highlow study

Low-molecular-weight heparin to prevent recurrent VTE in pregnancy: a randomized controlled trial of two doses

Summary

EudraCT number	2012-001505-24
Trial protocol	NL IE BE ES DK
Global end of trial date	31 October 2021

Results information

Result version number	v1 (current)
This version publication date	27 July 2023
First version publication date	27 July 2023
Summary attachment (see zip file)	Summary (Summary as published in the Lancet 2022.docx)

Trial information

Trial identification

Sponsor protocol code	2012-001505-24
-----------------------	----------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01828697
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amsterdamumc
Sponsor organisation address	Meibergdreef 9, Amsterdam, Netherlands,
Public contact	Project leader, AmsterdamUMC, +31 205669111na, saskia.middeldorp@radboudumc.nl
Scientific contact	Project leader, AmsterdamUMC, +31 205669111na, saskia.middeldorp@radboudumc.nl

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	31 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2021
Global end of trial reached?	Yes
Global end of trial date	31 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of intermediate dose LMWH versus fixed low dose LMWH in pregnant women with a history of previous VTE.

Protection of trial subjects:

Insurance

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 516
Country: Number of subjects enrolled	Norway: 28
Country: Number of subjects enrolled	Belgium: 42
Country: Number of subjects enrolled	Denmark: 15
Country: Number of subjects enrolled	Ireland: 99
Country: Number of subjects enrolled	France: 388
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Russian Federation: 3
Worldwide total number of subjects	1110
EEA total number of subjects	1088

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)	1110
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between April 24, 2013, and Oct 31, 2020, 1339 women were screened. 516 (46%) women were recruited from the Netherlands, 388 (35%) from France, 99 (9%) from Ireland, 42 (4%) from Belgium, 28 (3%) from Norway, 15 (1%) from Denmark, 12 (1%) from Canada, seven (1%) from the USA, and three (<1%) from Russia.

Pre-assignment

Screening details:

Between April 24, 2013, and Oct 31, 2020, 1339 women were screened. 516 (46%) women were recruited from the Netherlands, 388 (35%) from France, 99 (9%) from Ireland, 42 (4%) from Belgium, 28 (3%) from Norway, 15 (1%) from Denmark, 12 (1%) from Canada, seven (1%) from the USA, and three (<1%) from Russia.

Period 1

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

Blinding implementation details:

Eligible women were randomly assigned (1:1), using a web-based system and permuted block randomisation with a block size of six, stratified by centre, to weight-adjusted intermediate-dose or fixed low-dose low molecular-weight heparin once daily. Physicians and participants were unmasked to treatment allocation because medication was supplied by local pharmacies in usual patient care settings or as study drug in accordance with national regulatory requirements.

Arms

Are arms mutually exclusive?	Yes
Arm title	weight-adjusted intermediate dose LMWH

Arm description:

The intermediate-dose low-molecular-weight heparin regimen was approximately half of a therapeutic dose, categorised by actual bodyweight and adjusted if needed during pregnancy or post partum, with cutoffs of less than 50 kg, 50 kg to less than 70 kg, 70 kg to less than 100 kg, and 100 kg or more. Once-daily doses ranged from 3800 to 9500 international units (IU) for nadroparin, 6000 to 12 000 IU for enoxaparin, 7500 to 15 000 IU for dalteparin, or 4500 to 12 000 IU for tinzaparin.

Arm type	Active comparator
Investigational medicinal product name	Nadroparin, enoxaparin, dalteparin, tinzaparin
Investigational medicinal product code	
Other name	Fraxiparin, clexane, fragmin, innohep
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants were instructed to self-administer their allocated dose of low-molecular-weight heparin once daily from pre-filled syringes subcutaneously. The intermediate-dose low-molecular-weight heparin regimen was approximately half of a therapeutic dose, categorised by actual bodyweight and adjusted if needed during pregnancy or post partum, with cutoffs of less than 50 kg, 50 kg to less than 70 kg, 70 kg to less than 100 kg, and 100 kg or more. Once-daily doses ranged from 3800 to 9500 international units (IU) for nadroparin, 6000 to 12 000 IU for enoxaparin, 7500 to 15 000 IU for dalteparin, or 4500 to 12 000 IU for tinzaparin (table 1). The fixed low-dose regimen was based on bodyweight at randomisation (<100 kg or

≥100 kg), per clinical practice in many centres and suggested by the Royal College of Obstetricians and Gynaecologists' Green-top guideline and the dose was not changed throughout pregnancy or post partum.

Arm title	fixed low-dose LMWH
------------------	---------------------

Arm description:

The fixed low-dose regimen was based on bodyweight at randomisation (<100 kg or ≥100 kg), per clinical practice in many centres and suggested by the Royal College of Obstetricians and Gynaecologists' Green-top guideline, and the dose was not changed throughout pregnancy or post partum. The preferred type of low-molecular-weight heparin varied per centre.

Arm type	Active comparator
Investigational medicinal product name	Nadroparin, Dalteparin, Enoxaparin, Tinzaparin
Investigational medicinal product code	
Other name	Fraxiparin, Fragimin, Clexane, Innohep
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants were instructed to self-administer their allocated dose of low-molecular-weight heparin once daily from pre-filled syringes subcutaneously. The intermediate-dose low-molecular-weight heparin regimen was approximately half of a therapeutic dose, categorised by actual bodyweight and adjusted if needed during pregnancy or post partum, with cutoffs of less than 50 kg, 50 kg to less than 70 kg, 70 kg to less than 100 kg, and 100 kg or more. Once-daily doses ranged from 3800 to 9500 international units (IU) for nadroparin, 6000 to 12 000 IU for enoxaparin, 7500 to 15 000 IU for dalteparin, or 4500 to 12 000 IU for tinzaparin (table 1). The fixed low-dose regimen was based on bodyweight at randomisation (<100 kg or ≥100 kg), per clinical practice in many centres and suggested by the Royal College of Obstetricians and Gynaecologists' Green-top guideline and the dose was not changed throughout pregnancy or post partum.

Number of subjects in period 1	weight-adjusted intermediate dose LMWH	fixed low-dose LMWH
Started	555	555
Completed	555	555

Baseline characteristics

Reporting groups

Reporting group title	weight-adjusted intermediate dose LMWH
-----------------------	--

Reporting group description:

The intermediate-dose low-molecular-weight heparin regimen was approximately half of a therapeutic dose, categorised by actual bodyweight and adjusted if needed during pregnancy or post partum, with cutoffs of less than 50 kg, 50 kg to less than 70 kg, 70 kg to less than 100 kg, and 100 kg or more. Once-daily doses ranged from 3800 to 9500 international units (IU) for nadroparin, 6000 to 12 000 IU for enoxaparin, 7500 to 15 000 IU for dalteparin, or 4500 to 12 000 IU for tinzaparin

Reporting group title	fixed low-dose LMWH
-----------------------	---------------------

Reporting group description:

The fixed low-dose regimen was based on bodyweight at randomisation (<100 kg or ≥100 kg), per clinical practice in many centres and suggested by the Royal College of Obstetricians and Gynaecologists' Green-top guideline, and the dose was not changed throughout pregnancy or post partum. The preferred type of low-molecular-weight heparin varied per centre.

Reporting group values	weight-adjusted intermediate dose LMWH	fixed low-dose LMWH	Total
Number of subjects	555	555	1110
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 Units: years			
median	32	32	
standard deviation	± 4.8	± 4.8	-
Gender categorical Units: Subjects			
Female	555	555	1110
Male	0	0	0

Subject analysis sets

Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

We did the primary efficacy analysis in the intention-totreat (ITT) population, defined as all women

randomly assigned to treatment, and included all data and adjudicated outcomes from randomisation up to 6 weeks post partum.

Subject analysis set title	Safety analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

We assessed safety in all women who received at least one dose of allocated study treatment and who had a known date of end of on-treatment period, and included in our analyses all data and adjudicated outcomes from randomisation up to 6 weeks post partum.

Reporting group values	Intention to treat	Safety analysis	
Number of subjects	1110	1045	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	na	na	
standard deviation	±	±	
Gender categorical Units: Subjects			
Female	1110	1045	
Male	0	0	

End points

End points reporting groups

Reporting group title	weight-adjusted intermediate dose LMWH
-----------------------	--

Reporting group description:

The intermediate-dose low-molecular-weight heparin regimen was approximately half of a therapeutic dose, categorised by actual bodyweight and adjusted if needed during pregnancy or post partum, with cutoffs of less than 50 kg, 50 kg to less than 70 kg, 70 kg to less than 100 kg, and 100 kg or more. Once-daily doses ranged from 3800 to 9500 international units (IU) for nadroparin, 6000 to 12 000 IU for enoxaparin, 7500 to 15 000 IU for dalteparin, or 4500 to 12 000 IU for tinzaparin

Reporting group title	fixed low-dose LMWH
-----------------------	---------------------

Reporting group description:

The fixed low-dose regimen was based on bodyweight at randomisation (<100 kg or ≥100 kg), per clinical practice in many centres and suggested by the Royal College of Obstetricians and Gynaecologists' Green-top guideline, and the dose was not changed throughout pregnancy or post partum. The preferred type of low-molecular-weight heparin varied per centre.

Subject analysis set title	Intention to treat
----------------------------	--------------------

Subject analysis set type	Intention-to-treat
---------------------------	--------------------

Subject analysis set description:

We did the primary efficacy analysis in the intention-to-treat (ITT) population, defined as all women randomly assigned to treatment, and included all data and adjudicated outcomes from randomisation up to 6 weeks post partum.

Subject analysis set title	Safety analysis
----------------------------	-----------------

Subject analysis set type	Safety analysis
---------------------------	-----------------

Subject analysis set description:

We assessed safety in all women who received at least one dose of allocated study treatment and who had a known date of end of on-treatment period, and included in our analyses all data and adjudicated outcomes from randomisation up to 6 weeks post partum.

Primary: Primary efficacy outcome

End point title	Primary efficacy outcome
-----------------	--------------------------

End point description:

The primary efficacy outcome was symptomatic, objectively confirmed, venous thromboembolism (ie, a thromboembolism that is diagnosed by compression ultrasound examination, venography, CT or pulmonary angiography, or obduction and confirmed by the independent central adjudication committee) which was defined as an occurrence of new deep-vein thrombosis, pulmonary embolism, or unusual site venous thrombosis (eg, splanchnic vein or cerebral sinus thrombosis). After a diagnosis of recurrent thrombosis, patients were censored from the study.

End point type	Primary
----------------	---------

End point timeframe:

Any time from randomization up to 6 weeks postpartum

End point values	weight-adjusted intermediate dose LMWH	fixed low-dose LMWH	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	555	555	1110	
Units: number of events				
Pulmonary embolism	1	9	10	
DVT	8	6	14	
unusual site	2	1	3	

Statistical analyses

Statistical analysis title	statistical analysis primary efficacy
Statistical analysis description:	
We did the primary efficacy analysis in the intention-totreat (ITT) population, defined as all women randomly assigned to treatment, and included all data and adjudicated outcomes from randomisation up to 6 weeks post partum. Secondary efficacy analyses were also assessed in the ITT population. We also did prespecified analyses of the primary efficacy outcome from randomisation until 3 months post partum.	
Comparison groups	weight-adjusted intermediate dose LMWH v fixed low-dose LMWH
Number of subjects included in analysis	1110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05 ^[1]
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Notes:

[1] - we used the two-sided χ^2 test (or Fisher's exact test if fewer than five observations) to compare the intermediate-dose group with the low-dose group.

Primary: Primary safety outcome

End point title	Primary safety outcome
End point description:	
The primary safety outcome was major bleeding, which included antepartum, early post-partum (within 24 h after delivery), and late post-partum major bleeding (24 h or longer after delivery until 6 weeks post partum), based on population-specific definitions proposed by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH)	
End point type	Primary
End point timeframe:	
from randomisation up to 6 weeks postpartum	

End point values	weight-adjusted intermediate dose LMWH	fixed low-dose LMWH	Safety analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	520	525	1045	
Units: number of bleeding events				
Antepartum major bleeding	2	2	4	
Early post-partum	19	18	37	
Late post-partum	2	0	2	

Statistical analyses

Statistical analysis title	primary safety analysis
----------------------------	-------------------------

Statistical analysis description:

We assessed safety in all women who received at least one dose of allocated study treatment and who had a known date of end of on-treatment period, and included in our analyses all data and adjudicated outcomes from randomisation up to 6 weeks post partum. On-treatment was defined as the time from randomisation to the last day of allocated low-molecularweight heparin dose plus 2 days.

Comparison groups	weight-adjusted intermediate dose LMWH v fixed low-dose LMWH
Number of subjects included in analysis	1045
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05 [2]
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Notes:

[2] - For all outcomes, we used the two-sided χ^2 test (or Fisher's exact test if fewer than five observations) to compare the intermediate-dose group with the low-dose group.

Secondary: Secondary efficacy outcomes

End point title	Secondary efficacy outcomes
-----------------	-----------------------------

End point description:

Secondary efficacy outcomes were the three components of the primary outcome, objectively confirmed superficial thrombophlebitis, and a composite of venous thromboembolism or superficial thrombophlebitis,

End point type	Secondary
----------------	-----------

End point timeframe:

, at any time from randomisation until 6 weeks post partum, and until 3 months post partum.

End point values	weight-adjusted intermediate dose LMWH	fixed low-dose LMWH	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	555	555	1110	
Units: number of events	13	18	31	

Statistical analyses

No statistical analyses for this end point

Secondary: secondary safety outcomes

End point title	secondary safety outcomes
End point description:	
Secondary safety outcomes were a composite of major or clinically relevant non-major bleeding, clinically relevant non-major bleeding and minor bleeding using population-specific definitions, maternal mortality, bruises, skin reactions around the injection site (type IV allergy), type I allergic reaction to low-molecular weight heparin, heparin-induced thrombocytopenia and congenital anomalies or birth defects	
End point type	Secondary
End point timeframe:	
from randomization up to 6 weeks postpartum	

End point values	weight-adjusted intermediate dose LMWH	fixed low-dose LMWH	Safety analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	520	525	1045	
Units: number of events				
major or clinically relevant non-major bleeding	50	45	95	
clinically relevant non-major bleeding	27	25	52	
minor bleeding	76	66	142	
maternal mortality	0	0	0	
bruises	248	184	432	
type 1 skin reaction	8	2	10	
type 4 skin reaction	180	115	295	
congenital anomalies or birth defects	9	5	14	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

from randomization to 6 weeks postpartum

Adverse event reporting additional description:

This is a thromboprophylaxis study. SAE for the primary and secondary outcomes such as VTE mortality, congenital abnormalities, and bleeding, we refer to the primary and secondary efficacy and safety outcomes of the study.

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	not applicable
-----------------	----------------

Dictionary version	1
--------------------	---

Frequency threshold for reporting non-serious adverse events: 1 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: This is a thromboprophylaxis study. SAE/AE for the primary and secondary outcomes such as VTE, mortality, congenital abnormalities, and bleeding we refer to the primary and secondary efficacy and safety outcomes of the study.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36354038>