Clinical trial results:
Anticoagulants for Living FoEtuses in women with recurrent miscarriage and inherited thrombophilia : ALIFE 2

Summary

EudraCT number	2015-002357-35
Trial protocol	GB
Global end of trial date	25 November 2021

Results information

Result version number	v1 (current)
This version publication date	28 July 2023
First version publication date	28 July 2023

Trial information

Trial identification

Sponsor protocol code	SQ147214

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University Hospitals Coventry and Warwickshire NHS Trust
Sponsor organisation address	University Hospital, Clifford Bridge Road, Coventry, United Kingdom, CV22DX
Public contact	Warwick Clinical Trials Unit, University of Warwick, +44 024 7615 0478, ctuenquiries@warwick.ac.uk
Scientific contact	Warwick Clinical Trials Unit, University of Warwick, +44 024 7615 0478, ctuenquiries@warwick.ac.uk

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	20 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 November 2021
Global end of trial reached?	Yes
Global end of trial date	25 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of low molecular weight heparin (LMWH) in women with inherited thrombophilia who have experienced 2 or more recurrent miscarriages and/or intra-uterine foetal death.

Protection of trial subjects:

The trial was conducted in full conformance with the principles of the Declaration of Helsinki and ICH Good Clinical Practice (GCP) guidelines. The trial was reviewed and approved by the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). Participants were instructed on how to inject themselves with LMWH prior to administering their first dose of trial IMP. Refresher training was offered as appropriate.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 192
Country: Number of subjects enrolled	Netherlands: 134
Worldwide total number of subjects	326
EEA total number of subjects	134

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)	326
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 326 women were randomised to low-dose low-molecular-weight heparin or not, from 01/08/2012 to 30/01/2021 with a pause to recruitment due to the COVID-19 pandemic between 24/03/2020 to 09/06/2020. Women were registered and randomised from 40 sites across the Netherlands, the UK, the USA, Belgium, and Slovenia.

Pre-assignment

Screening details:

In the Netherlands coordinated sites, eligible women were first registered into the trial, and only consented and randomised into the trial once their pregnancy had been confirmed. In total 428 women were registered and 326 of those randomised. Reported results are for the 326 randomised only.

Period 1

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

Blinding implementation details:

Participants and physicians were not blinded as this was an open-label study. Outcome assessors were also not blinded to the trial arm allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard care

Arm description:

Standard pregnancy surveillance

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	LMWH

Arm description:

Low-molecular-weight Heparin administered

Arm type	Experimental
Investigational medicinal product name	Low Molecular Weight Heparins (LMWH)
Investigational medicinal product code	
Other name	Enoxaparin, Dalteparin, Tinzaparin
Pharmaceutical forms	Dispersion for injection in pre-filled syringe
Routes of administration	Injection

Dosage and administration details:

The investigational medicinal products in this study are enoxaparin, dalteparin and tinzaparin. All IMPs are classed as Low Molecular Weight Heparins (LMWH). LMWHs bind to anti-thrombin III leading to inhibition of coagulation factors IIa and Xa. Product of choice; Clexane (Sanofi-Aventis) Enoxaparin sodium 100mg/mL injection, 40mg in 0.4mL pre-filled syringe, or Inhixa (Techdow Pharma Ltd) Enoxaparin sodium 100mg/mL injection, 40mg in 0.4mL pre-filled syringe. If the treatment of choice is unavailable another type of LMWH in a dosage equivalent to Enoxaparin 40mg can be chosen from; Fragmin (Pfizer bv) Dalteparin sodium 25000 IU/ml injection, 5000 IU in 0.2mL pre-filled syringe, Innohep (Leo Pharma bv) Tinzaparin sodium 10000 IU/ml Injection, 4500 IU in 0.45mL pre-filled syringe.
Participants will be instructed in how to inject themselves subcutaneously once daily with a dose of LMWH in either upper leg or abdomen, prior to administering their first dose of trial IMP.

Number of subjects in period 1	Standard care	LMWH
Started	162	164
Completed	158	162
Not completed	4	2
Consent withdrawn by subject	3	1
Missing primary endpoint	-	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Standard care
Reporting group description: Standard pregnancy surveillance	
Reporting group title	LMWH
Reporting group description: Low-molecular-weight Heparin administered	

Reporting group values	Standard care	LMWH	Total
Number of subjects	162	164	326
Age categorical Units: Subjects			
>=36 years old	59	59	118
<36 years old	103	105	208
Age continuous Units: years			
arithmetic mean	33.3	33.5	
standard deviation	± 5.3	± 5.2	-
Gender categorical Units: Subjects			
Female	162	164	326
Male	0	0	0
Number of miscarriages			
Number of miscarriages participant had previously had at randomisation			
Units: Subjects			
2 miscarriages	52	46	98
3 or more miscarriages	110	118	228
Tertiary centre Units: Subjects			
Yes	139	143	282
No	23	21	44
Randomising study team Units: Subjects			
UK	96	96	192
Netherlands	66	68	134

End points

End points reporting groups	
Reporting group title	Standard care
Reporting group description: Standard pregnancy surveillance	
Reporting group title	LMWH
Reporting group description: Low-molecular-weight Heparin administered	

Primary: Live birth after 24+0 weeks gestation	
End point title	Live birth after 24+0 weeks gestation
End point description: Primary outcome measure was live birth after 24+0 weeks gestation	
End point type	Primary
End point timeframe: Live birth after 24+0 weeks gestation	

End point values	Standard care	LMWH		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	162		
Units: 320				
Live birth	112	116		
Pregnancy loss	46	46		

Statistical analyses

Statistical analysis title	Primary analysis (unadjusted)
Statistical analysis description: Unadjusted analysis reporting odds ratios (95% CI) and chi-squared p-value with continuity correction	
Comparison groups	LMWH v Standard care
Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99 [1]
Method	Chi-squared corrected
Parameter estimate	Odds ratio (OR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.68

Notes:

[1] - chi-squared p-value with continuity correction

Statistical analysis title	Primary analysis (adjusted)

Statistical analysis description:

Adjusted analysis reporting odds ratios (95% CI) and p-value using logistic regression adjusted for maternal age (<36 years, >=36 years), number of miscarriages (2, >=3), tertiary or non-tertiary centre, and randomising country (UK, Netherlands) with the standard surveillance group as the reference group

Comparison groups	Standard care v LMWH
Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.78

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from Randomisation (<7 weeks gestation) to end of trial (6-8 weeks post outcome). Serious adverse events were collected by UK only (N=192)

Adverse event reporting additional description:

AEs were collected systematically at the following intervals; 12 week visit, 24-26 week visit, 36 week visit, end of trial visit. An AE is defined as any untoward medical occurrence in a participant and which does not necessarily have a causal relationship with this treatment. Serious AEs were collected non-systematically throughout trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	4.0

Reporting groups

Reporting group title	Standard care

Reporting group description:

Standard pregnancy surveillance

Reporting group title	LMWH

Reporting group description:

Low-molecular-weight Heparin administered

Serious adverse events	Standard care	LMWH	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 162 (2.47%)	16 / 164 (9.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Congenital, familial and genetic disorders - other	Additional description: Imperforate anus and RDS in baby		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thromboembolic event			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Sinus tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy, puerperium and perinatal conditions - Other, specify	Additional description: (1)Meconium aspiration(2)Overnight admission-surgical management miscarriage(3)Surgical procedure-abdominal collection(4&5) Secondary PPH(6)Fetal decelerations via CTG(7)Spontaneous rupture of membrane &bleeding(8) Evac retained products of conception		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 162 (1.23%)	5 / 164 (3.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 162 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 162 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Reproductive system and breast disorders - Other, specify	Additional description: Salpingectomy		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleuritic pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 162 (0.62%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 162 (0.62%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 162 (0.62%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 162 (0.62%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychiatric disorders - Other, specify	Additional description: Severe bipolar disorder episode post delivery		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Uterine infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 162 (0.62%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial infection			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 162 (0.62%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Standard care	LMWH	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 162 (38.27%)	85 / 164 (51.83%)	
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences (all)	0	1	
Vascular disorders - Other, specify	Additional description: Vulval varicocity		
subjects affected / exposed	1 / 162 (0.62%)	0 / 164 (0.00%)	
occurrences (all)	1	0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy, puerperium and perinatal conditions - Other, specify	Additional description: (1) Cervix pessary (2) gestational hypertension (3-9) HELLP/or Pre-eclampsia (10) obstetric cholestasis (11-13) placental abruption		
subjects affected / exposed	6 / 162 (3.70%)	6 / 164 (3.66%)	
occurrences (all)	6	7	
General disorders and administration site conditions			
General disorders and administration site conditions - Other, specify	Additional description: (1) Fainting (2) Feeling unwell, braxston hicks, pale, clammy		

subjects affected / exposed	0 / 162 (0.00%)	2 / 164 (1.22%)	
occurrences (all)	0	2	
Injection site reaction			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	6 / 162 (3.70%)	7 / 164 (4.27%)	
occurrences (all)	6	10	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	2 / 162 (1.23%)	0 / 164 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders - Other, specify	Additional description: (1-49) antenatal bleed (50-70) post-partum bleed (71) PV bleed		
subjects affected / exposed	32 / 162 (19.75%)	30 / 164 (18.29%)	
occurrences (all)	37	34	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 162 (0.62%)	0 / 164 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	6 / 162 (3.70%)	7 / 164 (4.27%)	
occurrences (all)	7	8	
Respiratory, thoracic and mediastinal disorders - Other, specify	Additional description: Exacerbation of asthma		
subjects affected / exposed	1 / 162 (0.62%)	0 / 164 (0.00%)	
occurrences (all)	1	0	
Investigations			
Investigations - Other, specify	Additional description: (1) low papa (2-3) Scan for DVT (4) Vaginal discharge - green/brown		
subjects affected / exposed	4 / 162 (2.47%)	0 / 164 (0.00%)	
occurrences (all)	4	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 162 (0.62%)	1 / 164 (0.61%)	
occurrences (all)	1	1	

Injury, poisoning and procedural complications - Other, specify	Additional description: Spot of blood noted at injection site		
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences (all)	0	1	
Bruising			
subjects affected / exposed	12 / 162 (7.41%)	53 / 164 (32.32%)	
occurrences (all)	16	76	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 162 (0.00%)	3 / 164 (1.83%)	
occurrences (all)	0	3	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	2 / 162 (1.23%)	0 / 164 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders - Other, specify	Additional description: venous thromboembolism		
subjects affected / exposed	1 / 162 (0.62%)	0 / 164 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 162 (0.62%)	1 / 164 (0.61%)	
occurrences (all)	1	1	
Gastrointestinal disorders - Other, specify	Additional description: (1) abdominal pain (2) acid reflux (3) obstetric cholestasis (4) oral thrush		
subjects affected / exposed	1 / 162 (0.62%)	2 / 164 (1.22%)	
occurrences (all)	1	3	
Nausea			
subjects affected / exposed	1 / 162 (0.62%)	8 / 164 (4.88%)	
occurrences (all)	1	8	
Rectal haemorrhage			
subjects affected / exposed	1 / 162 (0.62%)	1 / 164 (0.61%)	
occurrences (all)	1	1	
Vomiting			

subjects affected / exposed	2 / 162 (1.23%)	2 / 164 (1.22%)	
occurrences (all)	2	2	
Skin and subcutaneous tissue disorders			
pregnancy associated rash			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders - Other, specify	Additional description: (1) brown spots on legs (2) Haemorrhoids (3-4) Itching (5-10) Mild skin reaction (11-12) Subcuticular bleed		
subjects affected / exposed	2 / 162 (1.23%)	9 / 164 (5.49%)	
occurrences (all)	2	10	
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences (all)	0	1	
Urinary incontinence			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorder - Other, specify	Additional description: (1) cramp (2) right leg sciatica		
subjects affected / exposed	0 / 162 (0.00%)	2 / 164 (1.22%)	
occurrences (all)	0	2	
Infections and infestations			
Infections and infestations - Other, specify	Additional description: (1-5) Chest infections (6) Ear infection (7) Infection of Perineal region (8) Shingles (9) Tonsillitis		
subjects affected / exposed	2 / 162 (1.23%)	6 / 164 (3.66%)	
occurrences (all)	2	7	
Tooth infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	3 / 162 (1.85%)	2 / 164 (1.22%)	
occurrences (all)	3	2	
Wound infection			
subjects affected / exposed	1 / 162 (0.62%)	3 / 164 (1.83%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	1 / 162 (0.62%)	0 / 164 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders - Other, specify	Additional description: Gestational diabetes		
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	
occurrences (all)	0	1	

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? Yes

Date	Interruption	Restart date
24 March 2020	Recruitment to the trial was paused for 3 months due to the COVID-19 pandemic.	09 June 2020

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37271152