Clinical trial results:
A Randomised Controlled Trial of the Efficacy and Mechanism of Levothyroxine Treatment on Pregnancy and Neonatal Outcomes in Women with Thyroid Antibodies. (TABLET: Thyroid AntiBodies and LEvoThyroxine Study)

Summary

EudraCT number	2011-000719-19
Trial protocol	GB
Global end of trial date	14 January 2019

Results information

Result version number	v1 (current)
This version publication date	30 June 2019
First version publication date	30 June 2019

Trial information

Trial identification

Sponsor protocol code	09/100/10

Additional study identifiers

ISRCTN number	ISRCTN15948785
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Room 119, Aston Webb Building, Edgbaston, Birmingham, United Kingdom, B15 2TT
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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	27 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 May 2018
Global end of trial reached?	Yes
Global end of trial date	14 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test the hypothesis that in women with normal thyroid function but with thyroid peroxidase antibodies (TPO), levothyroxine (50mcg, oral, once daily), started pre-conceptually and continued to the end of pregnancy, compared with placebo, increases the proportion of women who attain a live birth beyond 34 completed weeks of gestation by at least 10%.

Protection of trial subjects:

No special measures were required to minimise pain or distress in this patient population.

Background therapy:

A systematic review of 31 studies involving euthyroid women showed a strong association between the presence of thyroid peroxidase antibodies and miscarriage (odds ratio, 3.90; 95% confidence interval [CI], 2.48 to 6.12; P<0.001) and preterm birth (odds ratio, 2.07; 95% CI, 1.17 to 3.68; P = 0.01). Studies included in the systematic review involved women with recurrent miscarriage, infertile women, and unselected populations.

The 2017 guidelines of the American Thyroid Association stated that "insufficient evidence exists to conclusively determine whether LT4 [levothyroxine] therapy decreases pregnancy loss risk in TPOAb-positive [thyroid peroxidase antibody–positive] euthyroid women who are newly pregnant" and recommended that "administration of LT4 to TPOAb-positive euthyroid pregnant women with a . . . history of loss may be considered
given its potential benefits in comparison with its minimal risk." The guideline task force drew attention to our ongoing trial. We designed the
multicenter, randomized, placebo-controlled Thyroid Antibodies and Levothyroxine (TABLET) trial to investigate whether the use of levothyroxine would increase the rates of live births after at least 34 weeks of gestation among euthyroid women with thyroid peroxidase antibodies.

Evidence for comparator:

Participants were randomly assigned in a 1:1 ratio to receive oral capsules containing either 50 µg of levothyroxine or matched placebo once a day. Administration of the trial agents began immediately after randomization. The appearance, route, and timing of the administration of the trial agents were identical in the two groups. Throughout the duration of the trial, the participants, clinicians, and trial nurses were unaware of the trial-group assignments.

Actual start date of recruitment	01 September 2011
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: 952
Worldwide total number of subjects	952
EEA total number of subjects	952

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)	952
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The participants were recruited from 49 hospitals across the United Kingdom. 1420 were eligible for enrollment in the trial, of whom 952 consented to participate and were randomly assigned to receive either levothyroxine (476 women) or placebo (476 women).

Pre-assignment

Screening details:

A total of 19,556 women underwent tests to detect thyroid peroxidase antibodies and thyroid-function tests between December 2011 and January 2016. Of these women, 1420 were eligible for enrollment in the trial, of whom 952 consented to participate and were randomly assigned to receive either levothyroxine (476 women) or placebo (476 women).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Levothyroxine

Arm description:

50 µg of levothyroxine once a day.

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

Dosage and administration details:

oral capsules containing 50 µg of levothyroxine taken once a day.

Arm title	Placebo

Arm description:

Oral placebo taken once a day.

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

Dosage and administration details:

Oral placebo capsules taken once a day.

Number of subjects in period 1	Levothyroxine	Placebo
Started	476	476
Completed	470	470
Not completed	6	6
Lost to follow-up	6	6

Baseline characteristics

Reporting groups	
Reporting group title	Levothyroxine
Reporting group description:	
50 µg of levothyroxine once a day.	
Reporting group title	Placebo
Reporting group description:	
Oral placebo taken once a day.	

Reporting group values	Levothyroxine	Placebo	Total
Number of subjects	476	476	952
Age categorical Units: Subjects			
Adults (18-64 years)	476	476	952
Age continuous Units: years			
arithmetic mean	32.5	32.7	
standard deviation	± 4.9	± 4.9	-
Gender categorical Units: Subjects			
Female	476	476	952
Male	0	0	0
Ethnic group Units: Subjects			
White	328	337	665
Chinese	4	4	8
South Asian	110	94	204
Black	16	23	39
Other	18	18	36
Nulliparous Units: Subjects			
Nulliparous	141	131	272
Parous	335	342	677
Not recorded	0	3	3
Previous miscarriages Units: Subjects			
Zero	166	165	331
One or Two	219	213	432
Three or more	91	95	186
Not recorded	0	3	3
Previous preterm births at <34 wk Units: Subjects			
Yes	11	10	21
No	465	463	928
Not recorded	0	3	3
Current treatment for infertility Units: Subjects			

Yes	216	213	429
No	260	263	523
Serum thyrotropin level Units: Subjects			
≤2.5 mIU/liter	329	330	659
>2.5 mIU/liter	147	146	293
BMI Units: BMI			
arithmetic mean	26.4	26.5	
standard deviation	± 5.6	± 5.5	-
No. of previous miscarriages in women with ≥1 miscarriage Units: No. of previous miscarriages			
median	2	2	
inter-quartile range (Q1-Q3)	1 to 3	1 to 3	-
No. of previous miscarriages - first-trimester miscarriage (<14 wk) in women with ≥1 miscarriage Units: No. of previous miscarriages			
median	2	2	
inter-quartile range (Q1-Q3)	1 to 3	1 to 3	-
Serum thyrotropin level Units: mIU/liter			
median	2.10	2.01	
inter-quartile range (Q1-Q3)	1.51 to 2.74	1.45 to 2.70	-
Serum thyrotropin level (level on Log scale) Units: mIU/liter			
arithmetic mean	0.674	0.652	
standard deviation	± 0.422	± 0.418	-
Mean serum free thyroxine level Units: pmol/liter			
arithmetic mean	14.6	14.5	
standard deviation	± 1.9	± 2.0	-
Median serum thyroid peroxidase antibody level Units: IU/ml			
median	170	202	
inter-quartile range (Q1-Q3)	83 to 428	94 to 417	-

End points

End points reporting groups	
Reporting group title	Levothyroxine
Reporting group description: 50 µg of levothyroxine once a day.	
Reporting group title	Placebo
Reporting group description: Oral placebo taken once a day.	

Primary: Live birth ≥ 34 weeks	
End point title	Live birth ≥ 34 weeks
End point description:	
End point type	Primary
End point timeframe: From randomization to pregnancy end	

End point values	Levothyroxine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	470	470		
Units: Subjects	176	178		

Statistical analyses

Statistical analysis title	Log-binomial regression
Statistical analysis description: For the primary outcome (live birth at ≥34 weeks of gestation), the trial population consisted of all participants who underwent randomization (intention-to-treat population). Log-binomial regression was used to generate relative risks, with adjustment for the minimization variable for all binary outcomes.	
Comparison groups	Levothyroxine v Placebo
Number of subjects included in analysis	940
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.74
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.14

Variability estimate	Standard deviation

Secondary: Pregnancy at ≤12 mo after enrollment

End point title	Pregnancy at ≤12 mo after enrollment

End point description:

End point type	Secondary

End point timeframe:

Randomization to confirmation of pregnancy

End point values	Levothyroxine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	470	470		
Units: Subjects	266	274		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical pregnancy at 7 wk

End point title	Clinical pregnancy at 7 wk

End point description:

End point type	Secondary

End point timeframe:

Randomization to pregnancy end

End point values	Levothyroxine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266	274		
Units: Subjects	237	248		

Statistical analyses

No statistical analyses for this end point

Secondary: Ongoing pregnancy at 12 wk

End point title	Ongoing pregnancy at 12 wk

End point description:

End point type	Secondary

End point timeframe:
Randomization to pregnancy end

End point values	Levothyroxine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266	274		
Units: Subjects	194	200		

Statistical analyses

No statistical analyses for this end point

Secondary: Miscarriage at <24 wk

End point title	Miscarriage at <24 wk

End point description:

End point type	Secondary

End point timeframe:
Randomization to pregnancy end

End point values	Levothyroxine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266	274		
Units: Subjects	75	81		

Statistical analyses

No statistical analyses for this end point

Secondary: Stillbirth: intrauterine death at ≥24 wk

End point title	Stillbirth: intrauterine death at ≥24 wk

End point description:

End point type	Secondary

End point timeframe:
Randomization to pregnancy end

End point values	Levothyroxine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266	274		
Units: Subjects	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Ectopic pregnancy

End point title	Ectopic pregnancy

End point description:

End point type	Secondary

End point timeframe:

Randomization to pregnancy end

End point values	Levothyroxine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266	274		
Units: Subjects	3	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Termination of pregnancy

End point title	Termination of pregnancy

End point description:

End point type	Secondary

End point timeframe:

Randomization to pregnancy end

End point values	Levothyroxine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266	274		
Units: Subjects	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Live birth

End point title	Live birth

End point description:

End point type	Secondary

End point timeframe:

Randomization to pregnancy end

End point values	Levothyroxine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266	274		
Units: Subjects				
At <34 wk	10	10		
At ≥34 wk	176	178		

Statistical analyses

No statistical analyses for this end point

Secondary: Gestational age at delivery

End point title	Gestational age at delivery

End point description:

End point type	Secondary

End point timeframe:

Date of conception to pregnancy end

End point values	Levothyroxine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	188		
Units: Days				
arithmetic mean (standard deviation)	272 (± 17)	273 (± 18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Birth weight

End point title	Birth weight

End point description:

End point type	Secondary

End point timeframe:

Randomization to pregnancy end

End point values	Levothyroxine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	188		
Units: Grams				
arithmetic mean (standard deviation)	3226 (± 660)	3262 (± 668)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apgar score @ 1 minute

End point title	Apgar score @ 1 minute

End point description:

End point type	Secondary

End point timeframe:

Randomization to pregnancy end

End point values	Levothyroxine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	178		
Units: score				
median (inter-quartile range (Q1-Q3))	9 (9 to 9)	9 (8 to 9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apgar score @ 5 minutes

End point title	Apgar score @ 5 minutes

End point description:

End point type	Secondary

End point timeframe:

Randomization to pregnancy end

End point values	Levothyroxine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	178		
Units: score				
median (inter-quartile range (Q1-Q3))	9 (9 to 10)	9 (9 to 10)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From randomisation to pregnancy end or from randomisation to the end of 12 months of attempted conception

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	Levothyroxine
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

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: No non-serious adverse events were reported at a rate greater than 5%.

Serious adverse events	Levothyroxine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 470 (6.17%)	18 / 470 (3.83%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Anencephaly			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Edward's syndrome			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal tongue tie			
subjects affected / exposed	0 / 470 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal left sided duplex collecting system			

subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abdominal pain			
subjects affected / exposed	0 / 470 (0.00%)	4 / 470 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abnormal antenatal scan			
subjects affected / exposed	0 / 470 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back and epigastric pain			
subjects affected / exposed	0 / 470 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Placenta pracina			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Missed miscarriage			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Per vaginal bleeding			
subjects affected / exposed	1 / 470 (0.21%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-partum haemorrhage			
subjects affected / exposed	0 / 470 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right Iliac Fossa pain			

subjects affected / exposed	1 / 470 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Single fetal demise in twin pregnancy			
subjects affected / exposed	0 / 470 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spontaneous rupture of membranes			
subjects affected / exposed	0 / 470 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Facial weakness and numbness			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache and rash			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache, vomiting and tachycardia			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia and anxiety			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain and dysuria			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter infection			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
High blood pressure, nausea and vomiting			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Anxiety			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain and vomiting			
subjects affected / exposed	0 / 470 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest, back and stomach pains; shortness of breath			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exacerbation of asthma			
subjects affected / exposed	2 / 470 (0.43%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Enlarged thyroid and thyroid cysts			

subjects affected / exposed	0 / 470 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stage 1 papillary thyroid cancer			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgery			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Groin abscess			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Maternal sepsis			
subjects affected / exposed	0 / 470 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neonatal sepsis			
subjects affected / exposed	0 / 470 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 470 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-caesaerean infection			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis and neonatal hypogycaemia			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound tenderness, pyrexia and malaise			
subjects affected / exposed	1 / 470 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Levothyroxine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 470 (0.00%)	0 / 470 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2011	1. Protocol Version 2.0 Addition of members to steering committee and DMC. 2. Protocol Version 2.0 Addition of two further exclusion criteria. a) Women who intend to conceive using ovulation stimulation therapy. Women with ovulation stimulation treatment will have a very different hormonal milieu to those without ovarian stimulation. Thus the endocrinologists (and in fact one of the EME reviewers) suggested excluding these patients.b) Women with previous or current cardiac disease. Thyroxine has the effect of increasing heart rate, and will need to be carefully titrated in patients with cardiac disease. Thus this trial will not be suitable for them. 3. Protocol Version 2.0 Addition of Roche Cobas Analyser to specified Analysers for trial participation. 4. Protocol version 2.0 Additional appointment at 9 months post randomisation and pre-pregnancy to dispense a further 3 month supply of trial medication. This was previously covered by an appointment at 3 months post randomisation and pre pregnancy, where 6 months of medication was dispensed in one appointment. This extra appointment will overcome any potential problems involving drug expiry date of the IMP or Placebo and would also enable the trial investigators to meet with the participant and discuss any trial related issues. 5. Protocol version 2.0 Addition of collection of anonymised excess serum to be used for quality control purposes, and possible future analyses of other biomarkers, which we understand will require separate ethical approval. 6. Protocol Version 2.0 Minor changes in spelling, typos and table/section references.
24 November 2011	1. Protocol version 3.0 section 4.2 page 10 - In a double blind study there is no risk of foreknowledge, and therefore the sentence has been revised to read more clearly. 2. Protocol version 3.0 Section 5.1.4 page 11 - Revision of word "given" to "taken" as the capsule will be self-administered. The following sentence "A sheet giving instructions on how to take the capsules, and what to do if a capsule is missed, will be given to the participant at the randomisation appointment." has been inserted to inform of instructions sheet to take medication included in this submission. Deletion of sentence referring to attending clinician, as participant will be outpatient. 3. Protocol Version 3.0 section 5.3 page 12 re-arrangement of sentence - The Trial coordinator will monitor drug compliance with help from Pharmacy Accountability logs. 4. Protocol Version 3.0 section 8.3.1 Page 22 - removal of sentences "The Trial Statistician may be unblinded to the level of groups A and B. A and B will be made know to the DMC if appropriate" In section 5.5.3 the Trial Protocol does not specify statistician in the list of blinded people. In order to produce DMC reports at the A/B level, the trial Statistician would not be blinded. The following sentence has also been removed in line with this change.

04 April 2012	1.Target the Infertility population for screening and recruitment. 2.To increase the range of TFT analysers which are permitted for the trial. These are broadly the most frequently used analysers in the country. This will enable us to recruit from a wider range of centres. We have found that restricting to the Roche Analysers very limiting, meaning that other keen hospitals are not been given an opportunity to participate in the trial. The reference ranges for each analyser will be determined by the thyroid experts on the TMG. We feel that this change presents an opportunity to reflect the general UK population in the trial.To account for the variation in analysers we have also widened the Free T4 range Inclusion Criteria range to be between 10.0 to 21.0 pmol/L. 3.To allow for blood for screening to be taken at the first approach to the patient. (This is mainly at the request of the patients who would prefer their blood sample to be taken immediately with other bloods rather than having to return for a blood sample). 4.Removal of a DMC Member who has resigned from the trial DMC due to increasing trial commitments. (A replacement is being sought). 5.Listing specific examples of conditions which are not required to report an SAE.
25 September 2014	As timeframes for initial patient contact are short, and patients may be distressed, there are times when the patient is discharged before contact is made, even though they are aware of the trial. We wish to be able to contact the patient following discharge. We must exclude women with a current thyroid disorder, but do not want to exclude all women who have required only short-term treatment a significant time ago. It would be difficult to propose criteria for inclusion, so we propose that the small number of women who fall into this category are considered on a case by case basis, with discussion between the local PI and chief investigator. There is no safety reason to exclude these women. Patients who are initially screened for the trial are sometimes not contactable by telephone or will not answer calls from private numbers on their mobile phones. We wish to introduce a letter,to have the ability to contact patients with normal blood results by letter. We have introduced Patient Normal Results Letter v1.0 16/2/15 and amended the word "telephone" to "contact" in the Patient Screening Leaflet so it is now v5.0 16/2/15. Clarification that a trial number and treatment bottle are not allocated until all essential information is entered on to the randomisation database. We are explicitly mentioning that the randomisation algorithm will be minimised by centre. Given the study is double blind we do not believe this will be an issue. Adding the term pregnancy loss to clarify that all forms of pregnancy loss constitute an outcome of trial and that trial participation and trial drug use cease at this point. In a measure to gather good compliance data we are asking the trial participant a question on estimated percentage of time the IMP is taken, in addition to pill counting To clarify the clinical management of thyroid problems which are identified within the trial, we have re-worded some sections of the protocol and refer clinicians to guidance agreed by the TMG.
24 June 2015	Contents page amended to list Appendix I Summary of Product Characteristics. Section 6.1.4 changed wording. Appendix I changed wording to replace page on expected toxicities. Non Substantial Changes SmPC v3.0 24th June 2015 SmPC v4.0 25th June 2015 SmPC v5.0 26th June 2015
13 April 2016	Update the SmPC for the trial IMP Levothyroxine to 6.0
31 October 2016	Section: 4.2 update to the stratification variables. Sections: 5.1.3 clarification of the manufacturing authorisation holder to reflect the changes submitted in SA21.

04 October 2017	1.Update to the Trial Management Group. 2.Section 3.4.2 –Clarification to the exclusion criteria. 3.Section 5.1.1 -Clarification of safety assessments. 4.Section 5.1.3-Clarification on storage of IMP. 5.Section 5.2.1 –Clarification of treatment duration. 6.Section 5.3 –Clarification of compliance monitoring. 7.Section 5.5 –Clarification of withdrawal process. 8.Section 6.1.2/6.1.3/6.3/6.4 –Clarification of reporting SUSARs. 9.Section 7 –Clarification of follow up and secondary measures. 10.Section 8.1 –Clarification of primary outcome measure. 11.Section 8.3 –Clarification of statistical analysis. 12.Section 9.4 –Clarification of Date Monitoring and Ethics Committee. 13.Appendix I –updated SmPC for Levothyoxine.

Notes:

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/30907987