Clinical trial results:
Multi-modal effects of Thyroid hormone Replacement for Untreated older adults with Subclinical hypothyroidism; a randomised placebo-controlled Trial (TRUST)

Summary

EudraCT number	2011-004554-26
Trial protocol	GB IE NL
Global end of trial date	18 November 2016

Results information

Result version number	v1 (current)
This version publication date	17 April 2019
First version publication date	17 April 2019
Summary attachment (see zip file)	TRUST summary (2011-004554-26 summary.pdf)

Trial information

Trial identification

Sponsor protocol code	GN11GE272

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01660126
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NHS Greater Glasgow and Clyde
Sponsor organisation address	Dalnair Street, Glasgow, United Kingdom,
Public contact	Joanne McGarry, NHS Greater Glasgow and Clyde, Joanne.McGarry@ggc.scot.nhs.uk
Scientific contact	Joanne McGarry, NHS Greater Glasgow and Clyde, Joanne.McGarry@ggc.scot.nhs.uk
Sponsor organisation name	University of Glasgow
Sponsor organisation address	University Avenue, Glasgow, United Kingdom, G12 8QQ
Public contact	Dr Debra Stuart, University of Glasgow, debra.stuart@glasgow.ac.uk
Scientific contact	Dr Debra Stuart, University of Glasgow, debra.stuart@glasgow.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	18 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 November 2016
Global end of trial reached?	Yes
Global end of trial date	18 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

i. Does thyroxine treatment for SCH give multi-modal benefits for older people with SCH? ii. Are benefits seen across a wide range of outcomes, including prevention of cardiovascular disease, and improving health-related quality of life, muscle function and cognition? iii. Are benefits seen in specific subgroups of older people with SCH, including women, very elderly and those with mild degrees of SCH (TSH 4.6-10 mU/L)? iv. Are any benefits offset by adverse effects, such as atrial fibrillation or heart failure?

Protection of trial subjects:

To maintain levels of Thyroid Stimulating Hormone (TSH) within the reference range and avoid thyroxine overtreatment:
- very low thyroxine start dose (50 micrograms)
- regular Thyroid Function Tests
In addition:
- regular clinical review to identify and manage adverse events of special interest - cardiovascular (atrial fibrilliation, cardiac failure) and musculoskeletal (fractures and osteoporosis)
- regular assessment of hyperthyroid symptoms (ThyPRO)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2012
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	Netherlands: 255
Country: Number of subjects enrolled	United Kingdom: 150
Country: Number of subjects enrolled	Ireland: 115
Country: Number of subjects enrolled	Switzerland: 217
Worldwide total number of subjects	737
EEA total number of subjects	520

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)	0
From 65 to 84 years	685
85 years and over	52

Subject disposition

Recruitment

Recruitment details:

Recruitment took place in primary care practices and academic centres in four countries (the UK, Ireland, the Netherlands and Switzerland between March 2013 and December 2015.
Over 1000 General Practices agreed to take part, using clinical laboratory databases and practice records to identify potential study participants.

Pre-assignment

Screening details:

Screening according to:
Inclusion: age ≥ 65 yrs; persistent subclinical hypothyroidism measured at least twice
Exclusion: current levothyroxine/antithyroid drugs/amiodarone/lithium; thyroid surgery/radioactive iodine (12 mths); dementia; major illness/elective surgery/acute coronary syndrome (4 wks); terminal illness
2647 screened, 1910 excluded

Pre-assignment period milestones

Number of subjects started	737
Number of subjects completed	737

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

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:

A mock titration was performed in the placebo group using an adaptive schedule, in which the data centre allocated (by computer algorithm) the same proportion of placebo patients to dose adjustment (up or down) as required in the levothyroxine group.

Arm title	Levothyroxine

Arm description: -

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:

50 µg daily (or 25 µg in patients with a body weight of <50 kg or with known coronary heart disease [previous myocardial infarction or symptoms of angina pectoris])

Number of subjects in period 1	Placebo	Levothyroxine
Started	369	368
Underwent randomisation	369	368
Completed	369	368

Period 2

Period 2 title	Treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

All dose adjustments were generated and executed by means of computer without the intervention of a physician. The participants, investigators, and treating physicians were unaware of the results of thyrotropin measurements throughout the course of the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo

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:

A mock titration was performed in the placebo group using an adaptive schedule, in which the data centre allocated (by computer algorithm) the same proportion of placebo patients to dose adjustment (up or down) as required in the levothyroxine group

Arm title	Levothyroxine

Arm description:

Levothyroxine
Starting dose 50 µg daily (or 25 µg in patients with a body weight of <50 kg or with known coronary heart disease [previous myocardial infarction or symptoms of angina pectoris]) with dose adjustment aimed at maintaining thyrotropin level within the reference range (0.40 to 4.59 mIU per liter).

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:

Levothyroxine starting dose 50 µg daily (or 25 µg in patients with a body weight of <50 kg or with known coronary heart disease [previous myocardial infarction or symptoms of angina pectoris]). Dose adjustment was aimed to result in a thyrotropin level within the reference range (0.40 to 4.59 mIU per liter).

Number of subjects in period 2	Placebo	Levothyroxine
Started	369	368
12 month follow-up	337	332
Extended follow-up	187	194
Completed	187	194
Not completed	182	174
Physician decision	182	174

Baseline characteristics

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

Reporting group values	Placebo	Levothyroxine	Total
Number of subjects	369	368	737
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 at baseline			
Units: years			
arithmetic mean	74.8	74.0	
standard deviation	± 6.8	± 5.8	-
Gender categorical Units: Subjects			
Female	198	198	396
Male	171	170	341
Racial group			
Reported by the patient			
Units: Subjects			
White	362	362	724
Other	7	6	13
Housing			
Standard housing defined as non-sheltered community accommodation. By contrast, sheltered housing is purpose built, grouped housing for older persons, often with an on-site manager or warden.			
Units: Subjects			
Standard	356	358	714
Other	13	10	23
Ischemic heart disease			
Defined as a history of angina pectoris or previous myocardial infarction.			
Units: Subjects			
Yes	50	50	100
No or not recorded	319	318	637
Atrial fibrilliation Units: Subjects			

Yes	44	45	89
No or not recorded	325	323	648
Hypertension Units: Subjects			
Yes	183	192	375
No or Not recorded	186	176	362
Diabetes mellitus Units: Subjects			
Yes	54	63	117
No or Not recorded	315	305	620
Osteoporosis Units: Subjects			
Yes	47	41	88
No or Not recorded	322	327	649
Current smoking Units: Subjects			
Yes	33	29	62
No or Not recorded	336	339	675
Weight <50kg Units: Subjects			
Yes	5	5	10
No	364	363	727
Concomitant medicines Units: Number			
median	4	4	
inter-quartile range (Q1-Q3)	2 to 6	2 to 6	-
Mini-Mental State Examination score			
Score is on a scale from 0 to 30, with higher scores indicating better cognitive function.			
Units: Score			
median	29	29	
inter-quartile range (Q1-Q3)	28 to 30	27 to 30	-
Thyrotropin Units: mIU/L			
arithmetic mean	6.38	6.41	
standard deviation	± 2.01	± 2.01	-
Free thyroxine Units: pmol/L			
arithmetic mean	13.3	13.4	
standard deviation	± 1.9	± 2.1	-
Hypothyroid Symptoms score			
Assessed on a scale from 0 to 100, with a higher score indicating more symptoms			
Units: Score			
arithmetic mean	16.9	17.5	
standard deviation	± 17.9	± 18.8	-
Tiredness score			
From the Thyroid-Related Quality of Life Patient-Reported Outcome (ThyPRO) questionnaire. Assessed on a scale of 0 to 100, with a higher score indicating more tiredness.			
Units: Score			
arithmetic mean	25.5	25.9	
standard deviation	± 20.3	± 20.6	-
EQ-5D score			
The EuroQoL [EQ] Group 5-Dimension Self-Report Questionnaire (EQ-5D) descriptive index on a scale			

from −0.59 to 1.00; a higher score indicates better quality of life.			
Units: Score			
arithmetic mean	0.847	0.846	
standard deviation	± 0.171	± 0.187	-
EQ visual analogue scale score			
The EuroQoL [EQ] Group 5-Dimension Self-Report Questionnaire (EQ-5D) visual-analogue scale, on a scale from 0 to 100; a higher score indicates better quality of life.			
Units: Score			
arithmetic mean	76.5	78.4	
standard deviation	± 16.3	± 15.3	-
Hand grip strength			
Units: kg			
arithmetic mean	27.5	28.0	
standard deviation	± 11.3	± 10.2	-
Letter-digit coding test score			
The score on the letter–digit coding test (a test of executive cognitive function) indicates the speed of processing according to the number of correct responses in matching nine letters with nine digits in 90 seconds (minimum score is 0, with higher scores indicating better executive cognitive function; there is no maximum score).			
Units: Score			
arithmetic mean	25.2	24.9	
standard deviation	± 8.3	± 7.4	-
Systolic blood pressure			
Units: mm Hg			
arithmetic mean	140.4	141.2	
standard deviation	± 18.9	± 18.7	-
Diastolic blood pressure			
Units: mm Hg			
arithmetic mean	74.8	74.1	
standard deviation	± 11.7	± 11.6	-
Body Mass Index			
Weight in kilograms divided by the square of the height in meters.			
Units: score			
arithmetic mean	27.7	28.1	
standard deviation	± 4.6	± 5.3	-
Waist circumference			
Units: cm			
arithmetic mean	97.5	98.5	
standard deviation	± 12.8	± 13.6	-
Barthel Index			
The Barthel Index uses a scale from 0 to 20 points, with higher numbers indicating better performance on activities of daily living.			
Units: Score			
median	20	20	
inter-quartile range (Q1-Q3)	14 to 20	13 to 20	-
Instrumental Activities of Daily Living score			
The Instrumental Activities of Daily Living scale has a maximum score of 14 (range, 0 to 14), with higher scores indicating better performance in activities of daily living.			
Units: score			
median	14	14	
inter-quartile range (Q1-Q3)	7 to 14	7 to 14	-

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Levothyroxine
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Levothyroxine
Reporting group description: Levothyroxine Starting dose 50 µg daily (or 25 µg in patients with a body weight of <50 kg or with known coronary heart disease [previous myocardial infarction or symptoms of angina pectoris]) with dose adjustment aimed at maintaining thyrotropin level within the reference range (0.40 to 4.59 mIU per liter).	

Primary: Hypothyroid Symptoms score 12 months	
End point title	Hypothyroid Symptoms score 12 months
End point description: The range of the scale is 0 to 100, with a higher score indicating more symptoms. The minimum clinically important difference for each score has been estimated as 9 points.	
End point type	Primary
End point timeframe: 12 months	

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	318		
Units: Score				
arithmetic mean (standard deviation)	16.7 (± 17.5)	16.6 (± 16.9)		

Statistical analyses

Statistical analysis title	Hypothyroid Symptoms score
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99
Method	Regression, Linear

Confidence interval	
level	95 %
sides	2-sided

Primary: Tiredness score 12 months

End point title	Tiredness score 12 months

End point description:

The range of the scale is 0 to 100, with a higher score indicating more symptoms. The minimum clinically important difference for each score has been estimated as 9 points.

End point type	Primary

End point timeframe:

12 months

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	318		
Units: Score				
arithmetic mean (standard deviation)	28.6 (± 19.5)	28.7 (± 20.2)		

Statistical analyses

Statistical analysis title	Tiredness score

Statistical analysis description:

12 months

Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Primary: Hypothyroid Symptoms score Extended follow-up

End point title	Hypothyroid Symptoms score Extended follow-up

End point description:

End point type	Primary

End point timeframe:

Extended follow-up beyond 12 months was performed in a subgroup of patients. The median duration of

follow-up from baseline was [placebo] 24.2 months (interquartile range, 18.4 to 30.3) and [levothyroxine] 24.5 months (interquartile range, 18.4 to 30.5).

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	194		
Units: Score				
arithmetic mean (standard deviation)	15.2 (± 15.9)	17.9 (± 9.1)		

Statistical analyses

Statistical analysis title	Hypothyroid Symptoms score Extended follow-up
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Primary: Tiredness score Extended follow-up

End point title	Tiredness score Extended follow-up

End point description:

End point type	Primary

End point timeframe:

Extended follow-up beyond 12 months was performed in a subgroup of patients. The median duration of follow-up from baseline was [placebo] 24.2 months (interquartile range, 18.4 to 30.3) and [levothyroxine] 24.5 months (interquartile range, 18.4 to 30.5).

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	194		
Units: Score				
arithmetic mean (standard deviation)	31.9 (± 22.1)	30.2 (± 20.5)		

Statistical analyses

Statistical analysis title	Tiredness score Extended follow-up
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Secondary: EQ-5D descriptive score 12 months

End point title	EQ-5D descriptive score 12 months

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	318		
Units: Score				
arithmetic mean (standard deviation)	0.853 (± 0.191)	0.833 (± 0.212)		

Statistical analyses

Statistical analysis title	EQ-5D descriptive score
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Secondary: EQ VAS score 12 months

End point title	EQ VAS score 12 months

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	318		
Units: Score				
arithmetic mean (standard deviation)	77.4 (± 13.7)	77.3 (± 15.6)		

Statistical analyses

Statistical analysis title	EQ VAS score

Statistical analysis description:

12 months

Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Secondary: Hand grip strength 12 months

End point title	Hand grip strength 12 months

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	318		
Units: kg				
arithmetic mean (standard deviation)	27.1 (± 11.2)	27.5 (± 10.5)		

Statistical analyses

Statistical analysis title	Hand-grip strength
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Secondary: Systolic blood pressure 12 months

End point title	Systolic blood pressure 12 months
End point description:	
End point type	Secondary
End point timeframe: 12 months	

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	318		
Units: mm Hg				
arithmetic mean (standard deviation)	138.4 (± 17.8)	138.3 (± 18.7)		

Statistical analyses

Statistical analysis title	Systolic blood pressure
Comparison groups	Placebo v Levothyroxine

Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Secondary: Diastolic blood pressure 12 months

End point title	Diastolic blood pressure 12 months
End point description:	

End point type	Secondary
End point timeframe:	
12 months	

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	318		
Units: mm Hg				
arithmetic mean (standard deviation)	73.5 (± 11.1)	72.8 (± 11.4)		

Statistical analyses

Statistical analysis title	Diastolic blood pressure
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Secondary: Body Mass Index 12 months

End point title	Body Mass Index 12 months
End point description:	

End point type	Secondary

End point timeframe:
12 months

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	318		
Units: BMI				
arithmetic mean (standard deviation)	27.7 (± 4.6)	27.9 (± 5.1)		

Statistical analyses

Statistical analysis title	Body mass index
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.89
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Secondary: Waist circumference 12 months

End point title	Waist circumference 12 months

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	318		
Units: cm				
arithmetic mean (standard deviation)	96.8 (± 13.1)	98.0 (± 13.2)		

Statistical analyses

Statistical analysis title	Waist circumference
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Secondary: EQ-5D descriptive score Extended follow-up

End point title	EQ-5D descriptive score Extended follow-up

End point description:

End point type	Secondary

End point timeframe:

Extended follow-up beyond 12 months was performed in a subgroup of patients. The median duration of follow-up from baseline was [placebo] 24.2 months (interquartile range, 18.4 to 30.3) and [levothyroxine] 24.5 months (interquartile range, 18.4 to 30.5).

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	194		
Units: Score				
arithmetic mean (standard deviation)	0.829 (± 0.209)	0.864 (± 0.188)		

Statistical analyses

Statistical analysis title	EQ-5D descriptive score Extended follow-up
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Secondary: EQ VAS score Extended follow-up

End point title	EQ VAS score Extended follow-up

End point description:

End point type	Secondary

End point timeframe:

Extended follow-up beyond 12 months was performed in a subgroup of patients. The median duration of follow-up from baseline was [placebo] 24.2 months (interquartile range, 18.4 to 30.3) and [levothyroxine] 24.5 months (interquartile range, 18.4 to 30.5).

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	194		
Units: Score				
arithmetic mean (standard deviation)	77.2 (± 13.5)	76.8 (± 14.2)		

Statistical analyses

Statistical analysis title	EQ VAS score Extended follow-up
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Secondary: Hand grip strength Extended follow-up

End point title	Hand grip strength Extended follow-up

End point description:

End point type	Secondary

End point timeframe:

Extended follow-up beyond 12 months was performed in a subgroup of patients. The median duration of follow-up from baseline was [placebo] 24.2 months (interquartile range, 18.4 to 30.3) and [levothyroxine] 24.5 months (interquartile range, 18.4 to 30.5).

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	194		
Units: kg				
arithmetic mean (standard deviation)	24.9 (± 10.6)	24.4 (± 10.1)		

Statistical analyses

Statistical analysis title	Hand grip strength Extended follow-up
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Secondary: Systolic blood pressure Extended follow-up

End point title	Systolic blood pressure Extended follow-up

End point description:

End point type	Secondary

End point timeframe:

Extended follow-up beyond 12 months was performed in a subgroup of patients. The median duration of follow-up from baseline was [placebo] 24.2 months (interquartile range, 18.4 to 30.3) and [levothyroxine] 24.5 months (interquartile range, 18.4 to 30.5).

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	194		
Units: mm Hg				
arithmetic mean (standard deviation)	137.5 (± 19.2)	136.8 (± 17.6)		

Statistical analyses

Statistical analysis title	Systolic blood pressure Extended follow-up
Comparison groups	Placebo v Levothyroxine

Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Secondary: Diastolic blood pressure Extended follow-up

End point title	Diastolic blood pressure Extended follow-up

End point description:

End point type	Secondary

End point timeframe:

Extended follow-up beyond 12 months was performed in a subgroup of patients. The median duration of follow-up from baseline was [placebo] 24.2 months (interquartile range, 18.4 to 30.3) and [levothyroxine] 24.5 months (interquartile range, 18.4 to 30.5).

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	194		
Units: mm Hg				
arithmetic mean (standard deviation)	72.3 (± 11.4)	72.0 (± 11.5)		

Statistical analyses

Statistical analysis title	Diastolic blood pressure Extended follow-up
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Secondary: Body Mass Index Extended follow-up

End point title	Body Mass Index Extended follow-up

End point description:

End point type	Secondary

End point timeframe:

Extended follow-up beyond 12 months was performed in a subgroup of patients. The median duration of follow-up from baseline was [placebo] 24.2 months (interquartile range, 18.4 to 30.3) and [levothyroxine] 24.5 months (interquartile range, 18.4 to 30.5).

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	194		
Units: BMI				
arithmetic mean (standard deviation)	27.2 (± 4.5)	27.9 (± 4.9)		

Statistical analyses

Statistical analysis title	Body Mass Index Extended follow-up
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Secondary: Waist circumference Extended follow-up

End point title	Waist circumference Extended follow-up

End point description:

End point type	Secondary

End point timeframe:

Extended follow-up beyond 12 months was performed in a subgroup of patients. The median duration of follow-up from baseline was [placebo] 24.2 months (interquartile range, 18.4 to 30.3) and [levothyroxine] 24.5 months (interquartile range, 18.4 to 30.5).

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	194		
Units: cm				
arithmetic mean (standard deviation)	96.0 (± 13.8)	97.6 (± 13.4)		

Statistical analyses

Statistical analysis title	Waist circumference Extended follow-up
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Other pre-specified: Thyrotropin 12 months

End point title	Thyrotropin 12 months
End point description:	
End point type	Other pre-specified
End point timeframe: 12 months	

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	318		
Units: mIU/L				
arithmetic mean (standard deviation)	5.48 (± 2.48)	3.63 (± 2.11)		

Statistical analyses

Statistical analysis title	Thyrotropin
Statistical analysis description: Between group difference at 12 months	
Comparison groups	Placebo v Levothyroxine

Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Repeated measures regression
Confidence interval	
level	95 %
sides	2-sided

Other pre-specified: Hyperthyroid Symptoms score 12 months

End point title	Hyperthyroid Symptoms score 12 months

End point description:

The score on the Hyperthyroid Symptoms scale was recorded as a measure of possible adverse effects (on a scale from 0 to 100, with higher scores indicating more symptoms; minimum clinically important difference has been estimated as 9 points).

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	318		
Units: Score				
arithmetic mean (standard deviation)	10.3 (± 11.3)	10.5 (± 10.8)		

Statistical analyses

Statistical analysis title	Hyperthyroid Symptoms score
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.35
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Other pre-specified: Thyrotropin Extended follow-up

End point title	Thyrotropin Extended follow-up

End point description:

End point type	Other pre-specified

End point timeframe:

Extended follow-up beyond 12 months was performed in a subgroup of patients. The median duration of follow-up from baseline was [placebo] 24.2 months (interquartile range, 18.4 to 30.3) and [levothyroxine] 24.5 months (interquartile range, 18.4 to 30.5).

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	194		
Units: mIU/L				
arithmetic mean (standard deviation)	5.28 (± 2.50)	3.47 (± 2.08)		

Statistical analyses

Statistical analysis title	Thyrotropin Extended follow-up
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Other pre-specified: Hyperthyroid Symptoms score Extended follow-up

End point title	Hyperthyroid Symptoms score Extended follow-up

End point description:

End point type	Other pre-specified

End point timeframe:

Extended follow-up beyond 12 months was performed in a subgroup of patients. The median duration of follow-up from baseline was [placebo] 24.2 months (interquartile range, 18.4 to 30.3) and [levothyroxine] 24.5 months (interquartile range, 18.4 to 30.5).

End point values	Placebo	Levothyroxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	194		
Units: Score				
arithmetic mean (standard deviation)	9.8 (± 11.0)	11.1 (± 11.7)		

Statistical analyses

Statistical analysis title	Hyperthyroid Symptoms score Extended follow-up
Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46
Method	Regression, Linear
Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs that occur at any time after the inclusion of the subject in the study (defined as the time when the subject signs the informed consent) up to 30 days after the subject completed or discontinued the study will be reported.

Adverse event reporting additional description:

Adverse events of special interest (atrial fibrillation, heart failure, fracture, or new diagnosis of osteoporosis)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

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

Reporting group description: -

Serious adverse events	Placebo group	Levothyroxine group	
Total subjects affected by serious adverse events			
subjects affected / exposed	103 / 369 (27.91%)	78 / 368 (21.20%)	
number of deaths (all causes)	5	10	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
≥1 serious adverse event	Additional description: All systems		
subjects affected / exposed	103 / 369 (27.91%)	78 / 368 (21.20%)	
occurrences causally related to treatment / all	0 / 201	0 / 142	
deaths causally related to treatment / all	0 / 5	0 / 10	

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

Non-serious adverse events	Placebo group	Levothyroxine group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 369 (8.40%)	26 / 368 (7.07%)	
Cardiac disorders			
Atrial fibrillation	Additional description: New onset		
subjects affected / exposed	13 / 369 (3.52%)	11 / 368 (2.99%)	
occurrences (all)	24	24	

Cardiac failure			
subjects affected / exposed	6 / 369 (1.63%)	3 / 368 (0.82%)	
occurrences (all)	9	9	
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	8 / 369 (2.17%)	9 / 368 (2.45%)	
occurrences (all)	17	17	
Osteoporosis	Additional description: New diagnosis		
subjects affected / exposed	4 / 369 (1.08%)	3 / 368 (0.82%)	
occurrences (all)	7	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2012	Increase of TSH monitoring Reduction of starting dose to 25ug for some participants Change to 2 questionnaires Tablets rather than capsules Other minor changes
21 February 2014	Additional question to Thyrpro Lab flag BP time changed from baseline to screen
14 March 2014	Addition of UK research site
11 July 2014	Notification of new manufacturing sites
22 October 2015	Revision to projected recruitment numbers Protocol revision to reflect updated SmPC
19 January 2016	Inclusion of ThyPRO thyroid-specific quality of life assessment tool at final study visit.
24 March 2016	Details provided of process of patient and GP unblinding, and standard format notification letters

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/28402245