Clinical trial results:
THYRoxine in Acute Myocardial Infarction (ThyrAMI)

Summary

EudraCT number	2014-001369-28
Trial protocol	GB
Global end of trial date	10 December 2017

Results information

Result version number	v1 (current)
This version publication date	01 May 2020
First version publication date	01 May 2020

Trial information

Trial identification

Sponsor protocol code	880

Additional study identifiers

ISRCTN number	ISRCTN52505169
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	University Ref: BH120110

Notes:

Sponsors

Sponsor organisation name	Gateshead Health NHS Foundation Trust
Sponsor organisation address	Queen Elizabeth Avenue, Sheriff Hill, Gateshead, United Kingdom, NE9 6SX
Public contact	Salman Razvi, Gateshead Health NHS Foundation Trust, 44 01914456052, salman.razvi@nhs.net
Scientific contact	Salman Razvi, Gateshead Health NHS Foundation Trust, 44 01914456052, salman.razvi@nhs.net

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	10 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 December 2017
Global end of trial reached?	Yes
Global end of trial date	10 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

ThyrAMI-1: whether thyroid function at the time of heart attack is related to poorer heart disease outcomes.

ThyrAMI-2: to determine whether treatment of underactive thyroid with Levothyroxine following a heart attack improves heart muscle function.

The proposed sample size for ThyraAMI-1 (the observational study) was 2000 to 3000 participants and for ThyrAMI-2 (the RCT) 90 to 100 participants.

This report give the results for the randomised controlled trial which commenced recruitment in February 2015.

Protection of trial subjects:

ThyrAMI-1 was an observational study.
In ThyrAMI-2 any potential side effects of the IMP were described in the Participant Information Sheet and additionally explained during the consenting procedure. Levothyroxine is the treatment of choice for hypothyroidism and was not expected to cause any major side effects. Furthermore, the initial dose was low and was titrated by close monitoring of the participant's thyroid
function. Patient safety was monitored throughout study participation. All adverse events were recorded in patient notes and the electronic case report form. Additionally, any serious adverse events were specifically recorded and faxed using a secure electronic system, to the Chief Investigator and appropriate Newcastle Clinical Trials Unit staff and the Sponsor. In addition, an independent Data Monitoring and Efficacy Committee had oversight of the data generated from the trial on a regular basis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2015
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: 95
Worldwide total number of subjects	95
EEA total number of subjects	95

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)	54
From 65 to 84 years	41
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible participants were identified from acute hospitals. All individuals that matched the study criteria were approached, provided with a participant information sheet and informed consent obtained. Recruitment to ThyrAMI-2 took place between February 2015 and December 2016.

Pre-assignment

Screening details:

314 patients were screened for eligibility. 219 were excluded: TSH normalised 127; Refused 81; Contra Indication to MRI 3; Other interventional studies 8

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

Assignment to either the LT4 or placebo arm was blinded to the participant as well as study team (double-blind). The principal investigator at each site had the primary right to code assignment without the requirement to discuss breaking the code with the sponsor for a patient at their site.

Arms

Are arms mutually exclusive?	Yes
Arm title	Levothyroxine

Arm description:

Baseline

Arm type	Experimental
Investigational medicinal product name	Levothyroxine
Investigational medicinal product code	
Other name	Eltroxin, LT4
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Initial starting dose of LT4 will always be 25 mcg daily. To achieve the desired target TSH levels in the LT4 treated group (target TSH levels 0.5 – 2.5 mU/L), participants had their TSH levels checked regularly and concomitant dose of their LT4 altered by 25 mcg daily, if required. The IMP was provided as 5 week supplies of LT4 or matching placebo (dispensed separately at each visit), packaged into appropriate individual bottles (polypropylene).

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

Individuals in this group were given a fresh bottle of IMP starting at 4, 8, 12, 24 +/- 7 days after blood tests, to maintain the double blind.

Number of subjects in period 1	Levothyroxine	Placebo
Started	46	49
Completed	46	49

Period 2	
Period 2 title	52 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms	
Are arms mutually exclusive?	Yes
Arm title	Levothyroxine

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Levothyroxine
Investigational medicinal product code	
Other name	Eltroxin, LT4
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Initial starting dose of LT4 will always be 25 mcg daily. To achieve the desired target TSH levels in the LT4 treated group (target TSH levels 0.5 – 2.5 mU/L), participants had their TSH levels checked regularly and concomitant dose of their LT4 altered by 25 mcg daily, if required. The IMP was provided as 5 week supplies of LT4 or matching placebo (dispensed separately at each visit), packaged into appropriate individual bottles (polypropylene).

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

Individuals in this group were given a fresh bottle of IMP starting at 4, 8, 12, 24 +/- 7 days after blood tests, to maintain the double blind.

Number of subjects in period 2	Levothyroxine	Placebo
Started	46	49
Completed	39	46
Not completed	7	3
High BMI	1	-
Claustrophobia	2	1
Poor image quality	2	-
Died	1	1
Withdrew	1	1

Baseline characteristics

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

Reporting group values	Levothyroxine	Placebo	Total
Number of subjects	46	49	95
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			
arithmetic mean	64.1	62.9	
standard deviation	± 9.4	± 9.7	-
Gender categorical Units: Subjects			
Female	10	13	23
Male	36	36	72
Smoking status Units: Subjects			
Current smokers	14	11	25
Ex-smokers	21	16	37
Non-smokers	10	22	32
Missing	1	0	1
Diabetes mellitus Units: Subjects			
Yes	8	10	18
No	38	39	77
Hypercholesterolaemia Units: Subjects			
Yes	13	14	27
No	33	35	68
Cerebrovascular disease Units: Subjects			
Yes	2	3	5

No	44	46	90
Hypertension Units: Subjects			
Yes	18	19	37
No	28	30	58
Previous ischaemic heart disease Units: Subjects			
Yes	8	6	14
No	38	43	81
Coronary artery affected			
Baseline angioplasty characteristics by treatment allocation			
Units: Subjects			
Left main stem	0	2	2
LAD	11	18	29
RCA	22	23	45
Circumflex	7	5	12
Other	5	1	6
Not recorded	1	0	1
TIMI Flow pre-PCI			
Baseline angioplasty characteristics by treatment allocation			
Units: Subjects			
Grade 0	10	12	22
Grade 1	5	9	14
Grade 2	17	17	34
Grade 3	13	11	24
Not recorded	1	0	1
TIMI Flow post-PCI			
Baseline angioplasty characteristics by treatment allocation			
Units: Subjects			
Grade 2	3	2	5
Grade 3	42	47	89
Not recorded	1	0	1
Use of Glycoprotein 3b2a inhibitor			
Baseline angioplasty characteristics by treatment allocation			
Units: Subjects			
Yes	21	20	41
No	25	29	54
Subsequent staged PCI procedure			
Baseline angioplasty characteristics by treatment allocation			
Units: Subjects			
Yes	5	9	14
No	41	40	81
Drug eluting stent used during PCI			
Baseline angioplasty characteristics by treatment allocation			
Units: Subjects			
Yes	40	46	86
No	6	3	9
Systolic BP Units: mmHg			
arithmetic mean	127	126.3	
standard deviation	± 16.3	± 17.5	-

Diastolic BP			
Units: mmHg			
arithmetic mean	76	73.8	
standard deviation	± 8.6	± 10.6	-
Heart rate			
Units: bpm			
arithmetic mean	60.1	62.6	
standard deviation	± 9.5	± 9.2	-
TSH			
Units: mU/L			
median	5.75	5.7	
inter-quartile range (Q1-Q3)	4.95 to 7.05	4.7 to 7.3	-
FT4			
Units: pmol/L			
arithmetic mean	14.7	14.6	
standard deviation	± 2.1	± 2.5	-
FT3			
Units: pmol/L			
arithmetic mean	4.6	4.4	
standard deviation	± 0.8	± 0.6	-
Serum creatinine			
Units: umol/dl			
arithmetic mean	93.0	96.9	
standard deviation	± 36.5	± 66.2	-
Total cholesterol			
Units: mmol/L			
arithmetic mean	4.8	4.8	
standard deviation	± 1.3	± 1.2	-
Total ischaemia time			
Total ischaemia time for STEMI patients only			
Units: minutes			
median	120	137	
inter-quartile range (Q1-Q3)	81 to 172	72 to 209	-

End points

End points reporting groups	
Reporting group title	Levothyroxine
Reporting group description: Baseline	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Levothyroxine
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: LVEF	
End point title	LVEF
End point description: Change in left ventricular ejection fraction at 52 weeks, calculated from baseline and 52 week value.	
End point type	Primary
End point timeframe: 52 weeks	

End point values	Levothyroxine	Placebo	Levothyroxine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[1]	46[2]	39[3]	46[4]
Units: percent volume/volume				
arithmetic mean (standard deviation)	51.3 (± 9.1)	54.0 (± 7.9)	53.8 (± 9.7)	56.1 (± 7.9)

Notes:
[1] - Baseline
[2] - Baseline
[3] - 52 weeks
[4] - 52 weeks

Statistical analyses

Statistical analysis title	Adjusted difference between LT4 and placebo
Comparison groups	Levothyroxine v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.76

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	2.46

Secondary: LV volumes and function: EDV/BSA

End point title	LV volumes and function: EDV/BSA

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Levothyroxine	Placebo	Levothyroxine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[5]	46[6]	39[7]	46[8]
Units: ml/m2				
arithmetic mean (standard deviation)	68.6 (± 17.2)	70.5 (± 13.8)	66.7 (± 16.6)	70.4 (± 13.1)

Notes:

[5] - Baseline

[6] - Baseline

[7] - 52 weeks

[8] - 52 weeks

Statistical analyses

Statistical analysis title	Adjusted difference between LT4 and placebo

Statistical analysis description:

Primary and secondary outcomes were compared using linear regression adjusting for age, sex type of AMI, and baseline values.

Comparison groups	Levothyroxine v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-4.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.03
upper limit	0.49

Secondary: LV volumes and function: ESV/BSA

End point title	LV volumes and function: ESV/BSA

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Levothyroxine	Placebo	Levothyroxine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[9]	46[10]	39[11]	46[12]
Units: ml/m2				
arithmetic mean (standard deviation)	34.4 (± 14.1)	32.9 (± 9.9)	31.1 (± 12.1)	31.4 (± 10.2)

Notes:

[9] - Baseline

[10] - Baseline

[11] - 52 weeks

[12] - 52 weeks

Statistical analyses

Statistical analysis title	Adjusted difference between LT4 and placebo

Statistical analysis description:

Primary and secondary outcomes were compared using linear regression adjusting for age, sex type of AMI, and baseline values.

Comparison groups	Levothyroxine v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.46
upper limit	0.58

Secondary: LV volumes and function: Stroke volume

End point title	LV volumes and function: Stroke volume

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Levothyroxine	Placebo	Levothyroxine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[13]	46[14]	39[15]	46[16]
Units: ml				
arithmetic mean (standard deviation)	67.2 (± 13.1)	68.7 (± 16.1)	75.4 (± 16.7)	78.9 (± 15.9)

Notes:

[13] - Baseline

[14] - Baseline

[15] - 52 weeks

[16] - 52 weeks

Statistical analyses

Statistical analysis title	Adjusted difference between LT4 and placebo

Statistical analysis description:

Primary and secondary outcomes were compared using linear regression adjusting for age, sex type of AMI, and baseline values.

Comparison groups	Placebo v Levothyroxine
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-3.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.45
upper limit	0.94

Secondary: LV volumes and function: Stroke index

End point title	LV volumes and function: Stroke index

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Levothyroxine	Placebo	Levothyroxine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[17]	46[18]	39[19]	46[20]
Units: ml/m2				
arithmetic mean (standard deviation)	34.4 (± 6.6)	37.6 (± 7.9)	34.9 (± 7.8)	38.9 (± 6.9)

Notes:

[17] - Baseline

[18] - Baseline

[19] - 52 weeks

[20] - 52 weeks

Statistical analyses

Statistical analysis title	Adjusted difference between LT4 and placebo

Statistical analysis description:

Primary and secondary outcomes were compared using linear regression adjusting for age, sex type of AMI, and baseline values.

Comparison groups	Levothyroxine v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.11
upper limit	0.64

Secondary: LV volumes and function: Cardiac output

End point title	LV volumes and function: Cardiac output

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Levothyroxine	Placebo	Levothyroxine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[21]	46[22]	39[23]	46[24]
Units: L/min				
arithmetic mean (standard deviation)	3.9 (± 0.7)	4.6 (± 1.1)	4.1 (± 0.87)	4.6 (± 0.96)

Notes:
[21] - Baseline
[22] - Baseline
[23] - 52 weeks
[24] - 52 weeks

Statistical analyses

Statistical analysis title	Adjusted difference between LT4 and placebo

Statistical analysis description:

Primary and secondary outcomes were compared using linear regression adjusting for age, sex type of AMI, and baseline values.

Comparison groups	Levothyroxine v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.18

Secondary: LV volumes and function: Cardiac index

End point title	LV volumes and function: Cardiac index

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Levothyroxine	Placebo	Levothyroxine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[25]	46[26]	39[27]	46[28]
Units: L/min/m2				
arithmetic mean (standard deviation)	2.0 (± 0.3)	2.3 (± 0.5)	2.1 (± 0.43)	2.3 (± 0.38)

Notes:
[25] - Baseline
[26] - Baseline
[27] - 52 weeks
[28] - 52 weeks

Statistical analyses

Statistical analysis title	Adjusted difference between LT4 and placebo

Statistical analysis description:

Primary and secondary outcomes were compared using linear regression adjusting for age, sex type of AMI, and baseline values.

Comparison groups	Levothyroxine v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.09

Secondary: Infarct size

End point title	Infarct size

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Levothyroxine	Placebo	Levothyroxine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30[29]	30[30]	30[31]	30[32]
Units: gms				
median (inter-quartile range (Q1-Q3))	7.9 (2.5 to 20.3)	8.9 (1.9 to 16.1)	5.6 (1.3 to 15.2)	7.0 (1.0 to 13.3)

Notes:

[29] - Baseline

[30] - Baseline

[31] - 52 weeks

[32] - 52 weeks

Statistical analyses

Statistical analysis title	Adjusted difference between LT4 and placebo
Comparison groups	Levothyroxine v Placebo

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.31
upper limit	1.77

Secondary: LV mass

End point title	LV mass

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Levothyroxine	Placebo	Levothyroxine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30[33]	30[34]	30[35]	30[36]
Units: gms				
arithmetic mean (standard deviation)	106.4 (± 33.4)	102.1 (± 22.9)	99.2 (± 29.9)	94.0 (± 18.2)

Notes:

[33] - Baseline

[34] - Baseline

[35] - 52 weeks

[36] - 52 weeks

Statistical analyses

Statistical analysis title	Adjusted difference between LT4 and placebo
Comparison groups	Levothyroxine v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.54
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.43
upper limit	8.37

Secondary: Infarct size

End point title	Infarct size

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Levothyroxine	Placebo	Levothyroxine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30[37]	30[38]	30[39]	30[40]
Units: percentage				
median (inter-quartile range (Q1-Q3))	7.8 (2.7 to 14.7)	8.5 (1.7 to 16.2)	5.8 (2.1 to 12.9)	8.4 (1.0 to 14.8)

Notes:

[37] - Baseline

[38] - Baseline

[39] - 52 weeks

[40] - 52 weeks

Statistical analyses

Statistical analysis title	Adjusted difference between LT4 and placebo
Comparison groups	Levothyroxine v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	1.38

Secondary: SF12 Physical

End point title	SF12 Physical

End point description:

SF12 - Short Form Health status questionnaire.
Physical: scores range from 10 to 56, with higher scores indicating better physical health.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Levothyroxine	Placebo	Levothyroxine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45[41]	49[42]	45[43]	49[44]
Units: Scale score				
arithmetic mean (standard deviation)	39.9 (± 10.6)	38.5 (± 10.9)	46 (± 10.1)	45.6 (± 10.6)

Notes:

[41] - Baseline

[42] - Baseline

[43] - 52 weeks

[44] - 52 weeks

Statistical analyses

Statistical analysis title	Adjusted difference between LT4 and placebo
Comparison groups	Levothyroxine v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.54
upper limit	4.23

Secondary: SF12 Mental

End point title	SF12 Mental

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Levothyroxine	Placebo	Levothyroxine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45[45]	49[46]	45[47]	49[48]
Units: Scale score				
arithmetic mean (standard deviation)	49.6 (± 10.5)	38.5 (± 10.9)	50.4 (± 11.7)	52.8 (± 7.9)

Notes:

[45] - Baseline

[46] - Baseline

[47] - 52 weeks

[48] - 52 weeks

Statistical analyses

Statistical analysis title	Adjusted difference between LT4 and placebo
Comparison groups	Levothyroxine v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	-3.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	1.24

Secondary: MLWHF

End point title	MLWHF

End point description:

MLWHF - Minnesota Living With Heart Failure Questionnaire
Scores range from 0 to 105, with higher scores indicating increase in symptoms of heart failure.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Levothyroxine	Placebo	Levothyroxine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45[49]	49[50]	45[51]	49[52]
Units: Scale score				
median (inter-quartile range (Q1-Q3))	27.0 (12.3 to 40)	23.0 (11.5 to 37.5)	13.0 (6.8 to 24.3)	15.0 (6.0 to 30.0)

Notes:

[49] - Baseline

[50] - Baseline

[51] - 52 weeks
[52] - 52 weeks

Statistical analyses

Statistical analysis title	Adjusted difference between LT4 and placebo
Comparison groups	Levothyroxine v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	-3.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	3.08

Secondary: CESD

End point title	CESD

End point description:

CESD: Centre for Epidemiologic Studies Depression Scale.
Scores range from 0 to 60, with higher scores indicating greater depressive symptoms.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Levothyroxine	Placebo	Levothyroxine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45[53]	49[54]	45[55]	49[56]
Units: Scale score				
median (inter-quartile range (Q1-Q3))	9.0 (4.0 to 16.0)	8.0 (2.5 to 15.0)	10.0 (2.0 to 18.0)	5.0 (2.0 to 14.0)

Notes:
[53] - Baseline
[54] - Baseline
[55] - 52 weeks
[56] - 52 weeks

Statistical analyses

Statistical analysis title	Adjusted difference between LT4 and placebo
Comparison groups	Levothyroxine v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	3.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	6.27

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any serious adverse events were recorded throughout the duration of the trial until week 52 (+/- 3 days).

Adverse event reporting additional description:

All non-serious adverse events were recorded at the follow-up visits 2 – 6.

Assessment type	Systematic

Dictionary used

Dictionary name	Study specific
Dictionary version	1

Reporting groups

Reporting group title	Levothyroxine

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Levothyroxine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 46 (15.22%)	9 / 49 (18.37%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Cardiovascular events			
subjects affected / exposed	2 / 46 (4.35%)	5 / 49 (10.20%)	
occurrences causally related to treatment / all	1 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Non-cardiovascular events			
subjects affected / exposed	5 / 46 (10.87%)	4 / 49 (8.16%)	
occurrences causally related to treatment / all	0 / 8	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Levothyroxine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 46 (78.26%)	41 / 49 (83.67%)	
Cardiac disorders			
Cardiovascular events			
subjects affected / exposed	12 / 46 (26.09%)	17 / 49 (34.69%)	
occurrences (all)	15	18	
General disorders and administration site conditions			
Non-cardiovascular events			
subjects affected / exposed	24 / 46 (52.17%)	24 / 49 (48.98%)	
occurrences (all)	32	27	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2014	Addition of a second Product Licence (PL) Number for Levothyroxine 50 mcg tablets (PL16201/0001) Correction of a typographical error in the PL number for Levothyroxine 25 mcg, in the IMPD: PL12672/0016, corrected to PL12762/0016 Removal of the Product Licence Numbers from the trial protocol
13 March 2015	Change of PI at the Sunderland trial site.
30 March 2015	Change to inclusion/exclusion criteria for Thyrami-2 (protocol sections 15.1 & 15.2) Clarification of pharmacy unit which holds IMP bottle number allocation list to confirm site pharmacies remain blinded (protocol section 17.2) Removal of reference to code break envelopes (protocol section 19) Clarification and a point of consistency required for one of the non-clinical procedures in section A18 of the original REC form GP information letter amended to reflect changes to inclusion/exclusion criteria ISRCTN number added to protocol CSP reference added to protocol Minor administrative changes
08 June 2015	Addition of site – Leeds General Infirmary Removal of reference to Newcastle MR centre and RVI Clincal Research Facility in the PIS/ICF and protocol, in view of the addition of Leeds Reference to procedures only carried out at Newcastle and requirement of participants who are unable to attend Newcastle or have procedures locally to sign partial withdrawal form Minor administrative changes
17 August 2015	Additional of South Tees Hospital site.
13 January 2016	• Inclusion of ThyrAMI-1 genetic sub-study • New study documents relating to ThyrAMI-1 genetic sub-study • ThyrAMI-1 GP letter • Removal of pulse oximetry as ThyrAMI-2 study procedure • Clarification the Reference Safety Information for the study • Removal of SmPCs from protocol appendix • Minor administrative amendments

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported