



Clinical trial results:

Multicentre, controlled, randomised, open-label, cross-over clinical study of the efficacy and tolerability of L-thyroxine T4 soft capsules, in comparison to L-thyroxine tablets, in thyroidectomised patients.

Summary

EudraCT number	2006-002614-36
Trial protocol	IT FR
Global end of trial date	25 February 2010

Results information

Result version number	v1 (current)
This version publication date	12 November 2021
First version publication date	12 November 2021

Trial information

Trial identification

Sponsor protocol code	05ICHF/T407
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	IBSA
Sponsor organisation address	Via del Piano, Pambio-Noranco, Switzerland, 6915
Public contact	Giuseppe Mautone, IBSA, sd@ibsa.ch
Scientific contact	Giuseppe Mautone, IBSA, sd@ibsa.ch

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	23 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 February 2010
Global end of trial reached?	Yes
Global end of trial date	25 February 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study is to compare the therapeutic activity of L-thyroxine in soft capsule formulation for oral use with L-thyroxine in a tablet formulation.

Protection of trial subjects:

Patients were followed up according to the standard of care

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 May 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Italy: 179
Country: Number of subjects enrolled	Switzerland: 18
Worldwide total number of subjects	205
EEA total number of subjects	187

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)	182
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was done between April 2007 and February 2009 in all countries

Pre-assignment

Screening details:

236 subjects were screened on the basis of medical history and findings in the physical examination and laboratory investigations. 31 subjects failed screening for: noncompliance with inclusion/exclusion criteria, need for LT4 dose adjustment, not allowed therapy, voluntary withdrawal

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	LT4 soft capsule

Arm description:

daily treatment with LT4 soft capsules at the same dose as the subject was treated before

Arm type	Experimental
Investigational medicinal product name	L-thyroxine, soft capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Dose was variable and customised for each patient. Dose should have been kept constant throughout the duration of the study, with an initial dose being the same as that previously being taken before the study start, but changes within $\pm 35\%$ of the dose previously taken were allowed.

Arm title	LT4 tablet
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Arm description:

daily treatment with LT4 tablet at the same dose as the subject was treated before

Arm type	Active comparator
Investigational medicinal product name	L-thyroxine, tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dose was variable and customised for each patient. Dose should have been kept constant throughout the duration of the study, with an initial dose being the same as that previously being taken before the study start, but changes within $\pm 35\%$ of the dose previously taken were allowed

Number of subjects in period 1	LT4 soft capsule	LT4 tablet
Started	98	107
V2	97	104
Completed	95	102
Not completed	3	5
exclusion criterion	1	-
Consent withdrawn by subject	-	3
Adverse event, non-fatal	-	1
Lost to follow-up	2	1

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	LT4 soft capsule

Arm description:

daily treatment with LT4 soft capsules at the same dose as the subject was treated before

Arm type	Experimental
Investigational medicinal product name	L-thyroxine, soft capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Dose was variable and customised for each patient. Dose should have been kept constant throughout the duration of the study, with an initial dose being the same as that previously being taken before the study start, but changes within $\pm 35\%$ of the dose previously taken were allowed.

Arm title	LT4 tablets
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Arm description:

daily treatment with LT4 tablets at the same dose as the subject was treated before

Arm type	Active comparator
Investigational medicinal product name	L-thyroxine, tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dose was variable and customised for each patient. Dose should have been kept constant throughout the duration of the study, with an initial dose being the same as that previously being taken before the study start, but changes within $\pm 35\%$ of the dose previously taken were allowed

Number of subjects in period 2	LT4 soft capsule	LT4 tablets
Started	102	95
V4	99	94
Completed	98	93
Not completed	4	2
Consent withdrawn by subject	3	-
Adverse event, non-fatal	1	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Period 1
Reporting group description: all enrolled subjects	

Reporting group values	Period 1	Total	
Number of subjects	205	205	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	182	182	
From 65-84 years	23	23	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	50.56		
standard deviation	± 12.24	-	
Gender categorical			
Units: Subjects			
Female	152	152	
Male	53	53	

Subject analysis sets

Subject analysis set title	LT4 soft capsules
Subject analysis set type	Intention-to-treat

Subject analysis set description:

all randomised patients who received at least one dose of both the test and the reference treatment,
analysed for the cross-over period with LT4 soft capsules

Subject analysis set title	LT4 tablets
Subject analysis set type	Intention-to-treat

Subject analysis set description:

all randomised patients who received at least one dose of both the test and the reference treatment,
analysed for the cross-over period with LT4 tablets

Reporting group values	LT4 soft capsules	LT4 tablets	
Number of subjects	205	205	
Age categorical			
Units: Subjects			
In utero	0	0	

Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	182	182	
From 65-84 years	23	23	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	50.56	50.56	
standard deviation	± 12.24	± 12.24	
Gender categorical			
Units: Subjects			
Female	152	152	
Male	53	53	

End points

End points reporting groups

Reporting group title	LT4 soft capsule
Reporting group description: daily treatment with LT4 soft capsules at the same dose as the subject was treated before	
Reporting group title	LT4 tablet
Reporting group description: daily treatment with LT4 tablet at the same dose as the subject was treated before	
Reporting group title	LT4 soft capsule
Reporting group description: daily treatment with LT4 soft capsules at the same dose as the subject was treated before	
Reporting group title	LT4 tablets
Reporting group description: daily treatment with LT4 tablets at the same dose as the subject was treated before	
Subject analysis set title	LT4 soft capsules
Subject analysis set type	Intention-to-treat
Subject analysis set description: all randomised patients who received at least one dose of both the test and the reference treatment, analysed for the cross-over period with LT4 soft capsules	
Subject analysis set title	LT4 tablets
Subject analysis set type	Intention-to-treat
Subject analysis set description: all randomised patients who received at least one dose of both the test and the reference treatment, analysed for the cross-over period with LT4 tablets	

Primary: FT4-6 month

End point title	FT4-6 month
End point description: difference of serum levels of FT4 between start and end of a 6-month treatment period, analysed according to cross over design (equivalence bounds: +/- 2.57 pmol/L)	
End point type	Primary
End point timeframe: 6 months	

End point values	LT4 soft capsule	LT4 soft capsule	LT4 tablet	LT4 tablets
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	92	92	91
Units: pmol/L				
arithmetic mean (standard deviation)	-0.46 (± 2.53)	-0.81 (± 2.84)	-0.64 (± 2.03)	0.48 (± 2.41)

End point values	LT4 soft capsules	LT4 tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	183	183		

Units: pmol/L				
arithmetic mean (standard deviation)	-0.64 (± 2.69)	-0.08 (± 2.29)		

Statistical analyses

Statistical analysis title	ANCOVA-FT4-6 months
Statistical analysis description: analysis of covariance for cross-over design	
Comparison groups	LT4 soft capsules v LT4 tablets
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0786 ^[1]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06403
upper limit	1.173051

Notes:

[1] - the 95% confidence interval for the mean difference between the groups ranges from -0.06403 to 1.173051 and is well within the equivalence margins ±2.57

Secondary: FT3-6 month

End point title	FT3-6 month
End point description: difference between the serum levels of FT3 at start and end of the two treatment periods, analysed according to a crossover design	
End point type	Secondary
End point timeframe: 6 month	

End point values	LT4 soft capsule	LT4 soft capsule	LT4 tablet	LT4 tablets
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	92	92	91
Units: pmol/L				
arithmetic mean (standard deviation)	-0.04 (± 0.43)	-0.15 (± 0.45)	-0.00 (± 0.37)	-0.00 (± 0.43)

End point values	LT4 soft capsules	LT4 tablets		
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Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	183	183		
Units: pmol/L				
arithmetic mean (standard deviation)	-0.09 (± 0.44)	-0.00 (± 0.40)		

Statistical analyses

Statistical analysis title	ANCOVA-FT3-6 months
Statistical analysis description: analysis of covariance for cross-over design	
Comparison groups	LT4 soft capsules v LT4 tablets
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1067
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.088855
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.196987
upper limit	0.019277

Secondary: TSH-6 months

End point title	TSH-6 months
End point description: difference between the serum levels of TSH at start and end of the two treatment periods, analysed according to a crossover design	
End point type	Secondary
End point timeframe: 6 months	

End point values	LT4 soft capsule	LT4 soft capsule	LT4 tablet	LT4 tablets
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	92	92	91
Units: mU/L				
arithmetic mean (standard deviation)	0.204 (± 0.951)	0.501 (± 3.013)	0.322 (± 1.193)	-0.211 (± 1.112)

End point values	LT4 soft	LT4 tablets		
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	capsules			
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	183	183		
Units: mU/L				
arithmetic mean (standard deviation)	0.353 (\pm 2.238)	0.057 (\pm 1.181)		

Statistical analyses

Statistical analysis title	ANCOVA-TSH-6 months
Statistical analysis description: analysis of covariance for cross-over design	
Comparison groups	LT4 soft capsules v LT4 tablets
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1736
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.296553
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.724849
upper limit	0.131744

Secondary: dose-6 months

End point title	dose-6 months
End point description: daily T4 dose at the end of each treatment period	
End point type	Secondary
End point timeframe: 6 months	

End point values	LT4 soft capsules	LT4 tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	193	196		
Units: mcg				
arithmetic mean (standard deviation)	132.22 (\pm 32.60)	131.31 (\pm 31.90)		

Statistical analyses

Statistical analysis title	ANOVA-dose-6 months
Statistical analysis description: analysis of variance	
Comparison groups	LT4 soft capsules v LT4 tablets
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.4945
Method	ANOVA

Secondary: dose changes

End point title	dose changes
End point description: number of subjects experiencing dose changes	
End point type	Secondary
End point timeframe: throughout the treatment period	

End point values	LT4 soft capsules	LT4 tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	193	197		
Units: subjects	48	39		

Statistical analyses

Statistical analysis title	Chi square-dose changes
Statistical analysis description: chi square test on the number of subjects requiring changes in T4 daily dose during each treatment period	
Comparison groups	LT4 soft capsules v LT4 tablets
Number of subjects included in analysis	390
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2289
Method	Chi-squared

Secondary: metabolic control-hypothyroidism-6 month

End point title	metabolic control-hypothyroidism-6 month
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End point description: frequency of subjects displaying signs/symptoms of hypothyroidism at the end of the treatment period	
End point type	Secondary
End point timeframe: 6 month	

End point values	LT4 soft capsules	LT4 tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	193	195		
Units: subjects	0	0		

Statistical analyses

Statistical analysis title	Chi square-hypothyroidism
Statistical analysis description: Chi square test on the number of subjects with signs/symptoms of hypothyroidism at the end of the treatment period	
Comparison groups	LT4 soft capsules v LT4 tablets
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 1 [2]
Method	Chi-squared

Notes:

[2] - p value cannot be calculated because the result is 0 in both groups

Secondary: metabolic control-hyperthyroidism-6 month

End point title	metabolic control-hyperthyroidism-6 month
End point description: frequency of subjects displaying signs/symptoms of hyperthyroidism at the end of the treatment period	
End point type	Secondary
End point timeframe: 6 months	

End point values	LT4 soft capsules	LT4 tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	193	195		
Units: subjects	1	2		

Statistical analyses

Statistical analysis title	Chi square-hyperthyroidism
Statistical analysis description: Chi-square test on the number of subjects displaying signs/symptoms of hyperthyroidism at the end of the treatment period	
Comparison groups	LT4 soft capsules v LT4 tablets
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.5682
Method	Chi-squared

Secondary: patient satisfaction-6 month

End point title	patient satisfaction-6 month
End point description: patient satisfaction scored by subjects at the end of the treatment period	
End point type	Secondary
End point timeframe: 6 months	

End point values	LT4 soft capsules	LT4 tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	193	196		
Units: subjects				
fair	2	2		
good	130	158		
very good	61	36		

Statistical analyses

Statistical analysis title	Chi square-patient satisfaction
Statistical analysis description: Mantel-Haenszel Chi square for trend test on patient satisfaction evaluated at the end of the treatments cycles	
Comparison groups	LT4 soft capsules v LT4 tablets
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0038
Method	Mantel-Haenszel

Adverse events

Adverse events information

Timeframe for reporting adverse events:

whole study duration, from screening to final visit

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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Reporting groups

Reporting group title	LT4 soft capsule
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Reporting group description:

daily treatment with LT4 soft capsules at the same dose as the subject was treated before

Reporting group title	LT4 tablet
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Reporting group description:

daily treatment with LT4 tablet at the same dose as the subject was treated before

Serious adverse events	LT4 soft capsule	LT4 tablet	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 205 (0.49%)	3 / 205 (1.46%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Multiple fractures			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	1 / 205 (0.49%)	0 / 205 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine fibrosis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	LT4 soft capsule	LT4 tablet	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 205 (3.90%)	13 / 205 (6.34%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences (all)	0	1	
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Myomectomy			
subjects affected / exposed	1 / 205 (0.49%)	0 / 205 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 205 (0.98%)	0 / 205 (0.00%)	
occurrences (all)	2	0	

Reproductive system and breast disorders			
Uterine fibrosis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences (all)	0	1	
Metrorrhagia			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dry throat			
subjects affected / exposed	1 / 205 (0.49%)	0 / 205 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences (all)	0	1	
Nervousness			
subjects affected / exposed	0 / 205 (0.00%)	2 / 205 (0.98%)	
occurrences (all)	0	2	
Sleep disorder			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences (all)	0	1	
Investigations			
Weight increased			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences (all)	0	1	
Hand fracture			
subjects affected / exposed	1 / 205 (0.49%)	0 / 205 (0.00%)	
occurrences (all)	1	0	
Multiple fractures			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences (all)	0	1	
Pneumothorax traumatic			

subjects affected / exposed occurrences (all)	0 / 205 (0.00%) 0	1 / 205 (0.49%) 1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 205 (0.98%)	4 / 205 (1.95%)	
occurrences (all)	2	4	
Atrial fibrillation			
subjects affected / exposed	1 / 205 (0.49%)	0 / 205 (0.00%)	
occurrences (all)	1	0	
Cardiac failure			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Hypoaesthesia oral			
subjects affected / exposed	1 / 205 (0.49%)	0 / 205 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 205 (0.00%)	1 / 205 (0.49%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

none

Notes: