Clinical trial results:
Safety and bioavailability of Tirosint (Levothyroxine Sodium) Oral Solution administered as single dose with or without water in hypothyroid patients.

Summary

EudraCT number	2012-003677-25
Trial protocol	IT
Global end of trial date	29 April 2014

Results information

Result version number	v1 (current)
This version publication date	26 April 2017
First version publication date	26 April 2017

Trial information

Trial identification

Sponsor protocol code	12I/T405

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	IBSA INSTITUT BIOCHIMIQUE SA
Sponsor organisation address	Via del Piano P.O. Box 266, Pambio-Noranco, Switzerland, 6915
Public contact	R&D Scientific Affairs Administration & Archive Supervisor, IBSA INSTITUT BIOCHIMIQUE SA, +41 (0) 58 360 10 00, gabriella.gaglio@ibsa.ch
Scientific contact	R&D Scientific Affair Manager, IBSA INSTITUT BIOCHIMIQUE SA, +41 (0)58 360 10 00, claudia.scarsi@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	03 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 April 2014
Global end of trial reached?	Yes
Global end of trial date	29 April 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the absorption pattern of LT4, on the basis of circulating total T4 (TT4), in hypothyroid patients already treated with levothyroxine tablets, following the administration of levothyroxine sodium oral solution (LT4s) swallowed in fasting conditions with or without water.

Protection of trial subjects:

The patients were treated with two single doses of an already authorized LT4 solution at the therapeutic dose. However, in the hypothesis of an unforeseen increased absorption, an ECG was performed before study start and thereafter at the end of each treatment period. Vital signs were measured before and 24 hours after each dosing.
In addition, patients with seriously compromised cardiac (heart failure), hepatic, renal and/or respiratory functions; active arrhythmia or history of arrhythmia, particularly atrial fibrillation; serious metabolic (e.g. uncompensated diabetes mellitus), organs (e.g. cirrhosis of the liver), endocrine or systemic diseases (excluding the basic pathology); epilepsy; neoplastic pathology, active or in remission for less than 5 years (excluding the basic thyroid pathology) were excluded from the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 March 2013
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	Italy: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	18
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients scheduled for TSH stimulation test were selected or outpatients willing to comply with the protocol procedures. All of the subjects provided their written informed consent prior to the start of the screening visit.

Pre-assignment

Screening details:

The screening procedures included: demography; medical and medication history; general physical examination; vital signs (blood pressure [BP], heart rate [HR]); ECG; thyroid analyses (FT3; FT4, TSH, Tg, Tg-Ab); urine pregnancy test (in female subjects only), HIV and hepatitis B+C serology.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Levothyroxine oral solution administered with water

Arm description:

100 to 150 mcg of Levothyroxine oral solution was administered with a total amount of 240 mL water.

Arm type	Active comparator
Investigational medicinal product name	Tirosint® 25-50-100 µg / 1 mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

the content of 1 ampoule of levothyroxine sodium 100 (and 1 of 25 or 50, depending on current therapeutic dose) µg oral solution was squeezed in a glass and was diluted approximately in 140 mL of natural water at room temperature, the solution stirred with a spoon or stick and the patient drank the obtained solution. The glass was then rinsed twice with 50 mL of water, the solution stirred with the same spoon or stick and the patient drank both of the 50 ml solutions. Therefore the total amount of water consumed was 240 mL.

Arm title	Levothyroxine oral solution administered without water

Arm description:

100 to 150 mcg of Levothyroxine oral solution was administered directly in the mouth without water.

Arm type	Experimental
Investigational medicinal product name	Tirosint® 25-50-100 µg / 1 mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

the content of 1 ampoule of levothyroxine sodium 100 µg oral solution (and 1 of 25 or 50, depending on current therapeutic dose) was squeezed directly in the mouth.

Number of subjects in period 1	Levothyroxine oral solution administered with water	Levothyroxine oral solution administered without water
Started	18	18
Completed	18	18

Baseline characteristics

Reporting groups	
Reporting group title	Levothyroxine oral solution administered with water
Reporting group description:	
100 to 150 mcg of Levothyroxine oral solution was administered with a total amount of 240 mL water.	
Reporting group title	Levothyroxine oral solution administered without water
Reporting group description:	
100 to 150 mcg of Levothyroxine oral solution was administered directly in the mouth without water.	

Reporting group values	Levothyroxine oral solution administered with water	Levothyroxine oral solution administered without water	Total
Number of subjects	18	18	18
Age categorical			
Adults (18-64 years)			
Units: Subjects			
Adults (18-64 years)	18	18	18
Age continuous			
Units: years			
arithmetic mean	51.6	51.6	
standard deviation	± 9.2	± 9.2	-
Gender categorical			
Units: Subjects			
Female	15	15	15
Male	3	3	3

Subject analysis sets	
Subject analysis set title	PK Set
Subject analysis set type	Per protocol
Subject analysis set description:	
The PK set was defined as all randomised subjects who fulfilled the study protocol requirements in terms of investigational medicinal products intake and with evaluable data-sets of PK readouts for the scheduled treatment comparison, with no major deviations that could affect the PK results. This analysis set was used for the statistical analysis of the PK parameters.	

Reporting group values	PK Set		
Number of subjects	18		
Age categorical			
Adults (18-64 years)			
Units: Subjects			
Adults (18-64 years)	18		
Age continuous			
Units: years			
arithmetic mean	51.6		
standard deviation	± 9.2		

Gender categorical Units: Subjects			
Female	15		
Male	3		

End points

End points reporting groups

Reporting group title	Levothyroxine oral solution administered with water

Reporting group description:

100 to 150 mcg of Levothyroxine oral solution was administered with a total amount of 240 mL water.

Reporting group title	Levothyroxine oral solution administered without water

Reporting group description:

100 to 150 mcg of Levothyroxine oral solution was administered directly in the mouth without water.

Subject analysis set title	PK Set
Subject analysis set type	Per protocol

Subject analysis set description:

The PK set was defined as all randomised subjects who fulfilled the study protocol requirements in terms of investigational medicinal products intake and with evaluable data-sets of PK readouts for the scheduled treatment comparison, with no major deviations that could affect the PK results. This analysis set was used for the statistical analysis of the PK parameters.

Primary: Cmax

End point title	Cmax

End point description:

End point type	Primary

End point timeframe:

Serum concentrations of levothyroxine (TT4) were measured at:
-0.1 hours (= 6 minutes) pre-dose, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 24 hours post-dose.

End point values	Levothyroxine oral solution administered with water	Levothyroxine oral solution administered without water		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: ng/mL				
arithmetic mean (standard deviation)	103.64 (± 15.95)	100.59 (± 17.34)		

Statistical analyses

Statistical analysis title	90% CI

Statistical analysis description:

Analysis of variance (ANOVA) was performed for log-transformed unadjusted AUCs and Cmax. The oral solution ingested with water has been used as the reference formulation. The 90% confidence interval for the B/A ratio of the population means (solution without water/solution with water) were calculated.

Comparison groups	Levothyroxine oral solution administered with water v Levothyroxine oral solution administered without water

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	0.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.93
upper limit	1.01

Primary: AUC 0-24

End point title	AUC 0-24

End point description:

End point type	Primary

End point timeframe:

Serum concentrations of levothyroxine (TT4) were measured at:
-0.1 hours (= 6 minutes) pre-dose, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 24 hours post-dose.

End point values	Levothyroxine oral solution administered with water	Levothyroxine oral solution administered without water		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: ng/mL*h				
arithmetic mean (standard deviation)	2268.21 (± 393.9)	2253.6 (± 397.15)		

Statistical analyses

Statistical analysis title	90% CI

Statistical analysis description:

Analysis of variance (ANOVA) was performed for log-transformed unadjusted AUCs and Cmax. The oral solution ingested with water has been used as the reference formulation. The 90% confidence interval for the B/A ratio of the population means (solution without water/solution with water) was calculated.

Comparison groups	Levothyroxine oral solution administered with water v Levothyroxine oral solution administered without water

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	0.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.02

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Subjects were monitored for any untoward medical occurrences until safety check (10±3 days after the last IMP dosing). All untoward medical events were recorded in the adverse event section of the CRF.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Levothyroxine oral solution administered without water
Reporting group description: -	
Reporting group title	Levothyroxine oral solution administered with water

Reporting group description: -

Serious adverse events	Levothyroxine oral solution administered without water	Levothyroxine oral solution administered with water	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	0 / 18 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Levothyroxine oral solution administered without water	Levothyroxine oral solution administered with water	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
Musculoskeletal and connective tissue disorders			
Wrist fracture			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2013	Because the target number of 24 patients hadn't been reached, the recruitment period was extended beyond the date scheduled in the Study Protocol. In order to facilitate the recruitment of eligible patients, additional daily doses of levothyroxine were admitted beside 100 mcg/day, namely 125 and 150 mcg/day, provided that the patients were on stable treatment since at least 3 months on those doses. In order to obtain the daily doses of 125 and 150 mcg/day with the test product, additional strengths of Tirosint oral solution were provided. Since there were more than one dose involved in the study, the statistical analysis had been modified, by adding the grouping by dose of the descriptive statistics and the adjustment of individual PK parameters for the dose in the relevant sections of the study protocol. Following to changes in the Sponsor organigram, the Drug Safety Manager for this study was Chiara Godina. In the Study Protocol Version 2.0 changes resulting from NON-substantial Amendment N. 1 (change in the head of the clinical laboratory) and from NON-substantial Amendment N. 2 (change in the head of the clinical laboratory, and change in the location of the laboratory for TT4 assay) had been included. Moreover few typographical errors in the text had been corrected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
29 April 2014	In consequence of the delayed patients recruitment times and in agreement with the EMA guidelines, the Sponsor decided to stop the study on 11.06.2014, when 19 patients had been screened and 18 randomized and completed according to the protocol. Post-hoc evaluation of the type II error, showed that the statistical analysis was still conducted with a power >90% both in the PK set (18 subjects) and in the PK Control set (15 subjects).	-

Notes:

Limitations and caveats

None reported