



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 |
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Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 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

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|-----------------|--------|
| 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 | <p>Because the target number of 24 patients hadn't been reached, the recruitment period was extended beyond the date scheduled in the Study Protocol.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Following to changes in the Sponsor organigram, the Drug Safety Manager for this study was Chiara Godina.</p> <p>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.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---------------|--|--------------|
| 29 April 2014 | <p>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).</p> | - |

Notes:

Limitations and caveats

None reported