



Clinical trial results:

Clinical study of the efficacy of liquid (drops) versus classic (tablets) formulations of Levothyroxine in replacement therapy of congenital hypothyroidism in infancy and childhood

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2015-002462-24 |
| Trial protocol | GR |
| Global end of trial date | 07 November 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 20 November 2021 |
| First version publication date | 20 November 2021 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | T4drops-01 |
|-----------------------|------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories SA |
| Sponsor organisation address | 14th Km National Road 1, Kifissia, Greece, 14564 |
| Public contact | Regulatory Affairs department, Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories SA, 30 2108072512374, soumelas@uni-pharma.gr |
| Scientific contact | Regulatory Affairs department, Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories SA, 30 2108072512374, soumelas@uni-pharma.gr |

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 | 14 November 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 07 November 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 November 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of a new levothyroxine liquid formulation (T4® Oral drops, solution 100 ug / ml) versus the classic form (T4® Tablets) in infants and children who suffer from congenital hypothyroidism, during the study. The aim is to avoid a statistical difference between the results of hormonal measurements to the respective intervals between the two groups.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 01 December 2015 |
| 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 | Greece: 36 |
| Worldwide total number of subjects | 36 |
| EEA total number of subjects | 36 |

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) | 36 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study included children aged 4-12 years who have been diagnosed with Congenital Hypothyroidism by the National Program for Preventive Neonatal Screening which is conducted by the Institute of Child Health from March 2016 to November 2018. They are regularly monitored from their diagnosis in collaboration with the A Pediatric Clinic-Athens Univ.

Pre-assignment

Screening details:

- Age of 4-12 years old.
- Patients with diagnosed congenital hypothyroidism.
- Patients already on replacement therapy with T4® Tablets.
- TSH values 0.5-5 µU/mL at time of enrolment in the study

Period 1

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

Arms

| | |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group A-T4 Tablets |

Arm description:

Children aged 4-12 years old with congenital hypothyroidism, in which replacement therapy will continue with levothyroxine tablets (T4® Tablets).

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | T4 tablets |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The usual starting dosage of treatment during infancy is estimated at 10-15µg/Kg body weight/day and is adjusted in order for the T4 levels to remain within normal limits towards the upper third of the normal range for the respective age, and for TSH concentration to remain below 3µU / ml.

Levothyroxine tablets are dissolved in water for babies, toddlers and very young children and then given orally via a syringe.

| | |
|------------------|------------------|
| Arm title | Group B-T4 drops |
|------------------|------------------|

Arm description:

Children aged 4-12 years old with congenital hypothyroidism, in which replacement therapy will change to liquid form (T4® Oral drops, solution 100µg/ml)

| | |
|--|-----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | T4® Oral drops, solution 100µg/ml |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral drops, solution |
| Routes of administration | Oral use |

Dosage and administration details:

During this substitution the patient continues to receive in the liquid form the exact same levothyroxine dose as with the tablets, which has been proved to be the right dose for the individual patient

| Number of subjects in period 1 | Group A-T4 Tablets | Group B-T4 drops |
|--------------------------------|--------------------|------------------|
| Started | 17 | 19 |
| Completed | 17 | 19 |

Period 2

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

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group B-T4 drops |

Arm description:

Children aged 4-12 years old with congenital hypothyroidism, in which replacement therapy will change to liquid form (T4® Oral drops, solution 100µg/ml)

| | |
|--|-----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | T4® Oral drops, solution 100µg/ml |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral drops, solution |
| Routes of administration | Oral use |

Dosage and administration details:

During this substitution the patient continues to receive in the liquid form the exact same levothyroxine dose as with the tablets, which has been proved to be the right dose for the individual patient

| | |
|------------------|--------------------|
| Arm title | Group A-T4 Tablets |
|------------------|--------------------|

Arm description:

Children aged 4-12 years old with congenital hypothyroidism, in which replacement therapy will continue with levothyroxine tablets (T4® Tablets).

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | T4 tablets |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The usual starting dosage of treatment during infancy is estimated at 10-15µg/Kg body weight/day and is adjusted in order for the T4 levels to remain within normal limits towards the upper third of the normal range for the respective age, and for TSH concentration to remain below 3µU / ml. Levothyroxine tablets are dissolved in water for babies, toddlers and very young children and then given orally via a syringe.

| Number of subjects in period 2 | Group B-T4 drops | Group A-T4 Tablets |
|--------------------------------|------------------|--------------------|
| Started | 19 | 17 |
| Completed | 19 | 17 |

Period 3

| | |
|------------------------------|-------------------------|
| Period 3 title | Second visit-6 months |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group A-T4 Tablets |

Arm description:

Children aged 4-12 years old with congenital hypothyroidism, in which replacement therapy will continue with levothyroxine tablets (T4® Tablets).

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | T4 tablets |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The usual starting dosage of treatment during infancy is estimated at 10-15µg/Kg body weight/day and is adjusted in order for the T4 levels to remain within normal limits towards the upper third of the normal range for the respective age, and for TSH concentration to remain below 3µU / ml. Levothyroxine tablets are dissolved in water for babies, toddlers and very young children and then given orally via a syringe.

| | |
|------------------|------------------|
| Arm title | Group B-T4 drops |
|------------------|------------------|

Arm description:

Children aged 4-12 years old with congenital hypothyroidism, in which replacement therapy will change to liquid form (T4® Oral drops, solution 100µg/ml)

| | |
|--|-----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | T4® Oral drops, solution 100µg/ml |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral drops, solution |
| Routes of administration | Oral use |

Dosage and administration details:

During this substitution the patient continues to receive in the liquid form the exact same levothyroxine dose as with the tablets, which has been proved to be the right dose for the individual patient

| Number of subjects in period 3 | Group A-T4 Tablets | Group B-T4 drops |
|---------------------------------------|--------------------|------------------|
| Started | 17 | 19 |
| Completed | 17 | 19 |

Baseline characteristics

Reporting groups

| | |
|--|--------------------|
| Reporting group title | Group A-T4 Tablets |
| Reporting group description: Children aged 4-12 years old with congenital hypothyroidism, in which replacement therapy will continue with levothyroxine tablets (T4® Tablets). | |
| Reporting group title | Group B-T4 drops |
| Reporting group description: Children aged 4-12 years old with congenital hypothyroidism, in which replacement therapy will change to liquid form (T4® Oral drops, solution 100µg/ml) | |

| Reporting group values | Group A-T4 Tablets | Group B-T4 drops | Total |
|---|--------------------|------------------|-------|
| Number of subjects | 17 | 19 | 36 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 17 | 19 | 36 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 6.8 | 8.9 | - |
| standard deviation | ± 2.1 | ± 2.3 | - |
| Gender categorical Units: Subjects | | | |
| Female | 7 | 8 | 15 |
| Male | 10 | 11 | 21 |
| Weight Units: kilogram(s) | | | |
| arithmetic mean | 26.97 | 33.43 | - |
| standard deviation | ± 10.37 | ± 12.84 | - |
| Height Units: centimeter | | | |
| arithmetic mean | 122.38 | 132.10 | - |
| standard deviation | ± 14.55 | ± 14.99 | - |
| BMI Units: kilogram(s)/square meter | | | |
| arithmetic mean | 17.94 | 18.43 | - |
| standard deviation | ± 3.56 | ± 3.45 | - |
| Starting dose Units: µg/kg/d | | | |
| arithmetic mean | 1.8 | 1.4 | |

| | | | |
|--------------------|--------|--------|---|
| standard deviation | ± 0.6 | ± 0.6 | - |
| TSH | | | |
| Units: µIU/ml | | | |
| arithmetic mean | 3.31 | 3.24 | |
| standard deviation | ± 1.09 | ± 0.86 | - |
| FT4 | | | |
| Units: pg/ml | | | |
| arithmetic mean | 13.79 | 13.59 | |
| standard deviation | ± 2.61 | ± 2.08 | - |

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | Group A-T4 Tablets |
| Reporting group description: Children aged 4-12 years old with congenital hypothyroidism, in which replacement therapy will continue with levothyroxine tablets (T4® Tablets). | |
| Reporting group title | Group B-T4 drops |
| Reporting group description: Children aged 4-12 years old with congenital hypothyroidism, in which replacement therapy will change to liquid form (T4® Oral drops, solution 100µg/ml) | |
| Reporting group title | Group B-T4 drops |
| Reporting group description: Children aged 4-12 years old with congenital hypothyroidism, in which replacement therapy will change to liquid form (T4® Oral drops, solution 100µg/ml) | |
| Reporting group title | Group A-T4 Tablets |
| Reporting group description: Children aged 4-12 years old with congenital hypothyroidism, in which replacement therapy will continue with levothyroxine tablets (T4® Tablets). | |
| Reporting group title | Group A-T4 Tablets |
| Reporting group description: Children aged 4-12 years old with congenital hypothyroidism, in which replacement therapy will continue with levothyroxine tablets (T4® Tablets). | |
| Reporting group title | Group B-T4 drops |
| Reporting group description: Children aged 4-12 years old with congenital hypothyroidism, in which replacement therapy will change to liquid form (T4® Oral drops, solution 100µg/ml) | |

Primary: TSH-T4 tablets

| | |
|---|-------------------------------|
| End point title | TSH-T4 tablets ^[1] |
| End point description: | |
| End point type | Primary |
| End point timeframe: At 6 months visit | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: N/A | |

| End point values | Group A-T4 Tablets | | | |
|--------------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 17 | | | |
| Units: µIU/ml | | | | |
| arithmetic mean (standard deviation) | 4.42 (± 1.43) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: TSH-Oral drops

End point title TSH-Oral drops^[2]

End point description:

End point type Primary

End point timeframe:

At 2 months visit

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: N/A

| End point values | Group B-T4 drops | | | |
|--------------------------------------|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 19 | | | |
| Units: µIU/ml | | | | |
| arithmetic mean (standard deviation) | 4.46 (± 2.05) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: TSH-Oral drops

End point title TSH-Oral drops^[3]

End point description:

End point type Primary

End point timeframe:

At 6 months visit

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: N/A

| End point values | Group B-T4 drops | | | |
|--------------------------------------|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 19 | | | |
| Units: µIU/ml | | | | |
| arithmetic mean (standard deviation) | 3.25 (± 1.51) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: FT4-T4 tablets

| | |
|-----------------|-------------------------------|
| End point title | FT4-T4 tablets ^[4] |
|-----------------|-------------------------------|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At 6 months visit

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: N/A

| End point values | Group A-T4 Tablets | | | |
|--------------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 17 | | | |
| Units: pg/ml | | | | |
| arithmetic mean (standard deviation) | 13.57 (± 2.01) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: FT4-Oral drops

| | |
|-----------------|-------------------------------|
| End point title | FT4-Oral drops ^[5] |
|-----------------|-------------------------------|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At 2 months visit

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: N/A

| End point values | Group B-T4 drops | | | |
|--------------------------------------|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 19 | | | |
| Units: pg/ml) | | | | |
| arithmetic mean (standard deviation) | 13.58 (± 1.75) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: FT4-Oral drops

| | |
|-----------------|-------------------------------|
| End point title | FT4-Oral drops ^[6] |
|-----------------|-------------------------------|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At 6 months visit

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: N/A

| | | | | |
|--------------------------------------|------------------|--|--|--|
| End point values | Group B-T4 drops | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 19 | | | |
| Units: pg/ml) | | | | |
| arithmetic mean (standard deviation) | 13.06 (± 2.07) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

6 months treatment

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | End of trial |
|-----------------------|--------------|

Reporting group description: -

| Serious adverse events | End of trial | | |
|---|---------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

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

| Non-serious adverse events | End of trial | | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| Gastrointestinal disorders | | | |
| Dyspepsia | Additional description: Heartburn afetr receiving the oral drops | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences (all) | 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

None reported