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