Clinical trial results:
Clinical study of the efficacy of liquid (drops) versus classic (tablets) formulations of levothyroxine in replacement therapy of adults with clinical hypothyroidism.

Summary

EudraCT number	2017-001760-38
Trial protocol	GR
Global end of trial date	31 October 2018

Results information

Result version number	v1 (current)
This version publication date	14 November 2021
First version publication date	14 November 2021
Summary attachment (see zip file)	DOI: 10.1159/000508216 (Therapeutic Equivalence of a New Preparation.pdf)

Trial information

Trial identification

Sponsor protocol code	T4drops-02

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 S.A., 30 2108072512374, soumelas@uni-pharma.gr
Scientific contact	Regulatory Affairs department, Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A., 2108072512 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	01 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2018
Global end of trial reached?	Yes
Global end of trial date	31 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Scope of the present study is to investigate whether there is equivalent efficacy between replacement therapy of a new LT4 formulation in liquid form (oral drops) versus the classic form (tablets) in adult patients with clinical permanent hypothyroidism.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator:

Use of the tablet Levothyroxine formulation of the same manufacturer (T4® tablets by Uni-Pharma).

Actual start date of recruitment	31 August 2017
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: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	50
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was admitted to the study on 19.09.2017 and the date of last visit of last patient was 31.10.2018.

Pre-assignment

Screening details:

1. Patients diagnosed with clinically permanent hypothyroidism
2. 20-60 years
3. Patients who are already receiving replacement therapy with levothyroxine tablets
At the time of screening, many of the patients were taking levo tablets other than T4® so due to possible different bioequivalence between the products, patients were switched to T4®

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Tablets

Arm description:

The levothyroxine preparation that the patient was receiving prior to entering the study was switched to T4® tablets (group A), , in the same dose

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:

At the same dosage the patients used to receive prior to entering the study

Arm title	T4 Oral drops

Arm description:

The levothyroxine preparation that the patient was receiving prior to entering the study was switched either to T4® drops (group B), in the same dose

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

Dosage and administration details:

At the same Levothyroxine dose the patient was receiving prior to entering the study

Number of subjects in period 1	Tablets	T4 Oral drops
Started	25	25
Completed	22	22
Not completed	3	3
Lost to follow-up	3	3

Period 2

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

Arms

Are arms mutually exclusive?	No
Arm title	T4 Tablets

Arm description:

At the second visit, if the TSH levels were within the target range, the patient was switched from the tablet to the liquid form with the same dose

Arm type	Active comparator
Investigational medicinal product name	T4 100µg/ml oral drops, solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

At the second visit, if the TSH levels were within the target range, the patient was switched from the tablet to the liquid form with the same dose

Arm title	T4 Oral drops

Arm description:

At the second visit, if the TSH levels were within the target range, the patient was switched from the oral drops to the tablet form with the same dose

Arm type	Experimental
Investigational medicinal product name	T4 tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

At the second visit, if the TSH levels were within the target range, the patient was switched from the oral drops to the tablet form with the same dose

Number of subjects in period 2	T4 Tablets	T4 Oral drops
Started	22	22
Completed	21	18
Not completed	1	4
Protocol deviation	1	4

Baseline characteristics

Reporting groups	
Reporting group title	First visit

Reporting group description: -

Reporting group values	First visit	Total	
Number of subjects	50	50	
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)	50	50	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	42.4		
standard deviation	± 12.5	-	
Gender categorical Units: Subjects			
Female	41	41	
Male	9	9	

End points

End points reporting groups

Reporting group title	Tablets

Reporting group description:

The levothyroxine preparation that the patient was receiving prior to entering the study was switched to T4® tablets (group A), , in the same dose

Reporting group title	T4 Oral drops

Reporting group description:

The levothyroxine preparation that the patient was receiving prior to entering the study was switched either to T4® drops (group B), in the same dose

Reporting group title	T4 Tablets

Reporting group description:

At the second visit, if the TSH levels were within the target range, the patient was switched from the tablet to the liquid form with the same dose

Reporting group title	T4 Oral drops

Reporting group description:

At the second visit, if the TSH levels were within the target range, the patient was switched from the oral drops to the tablet form with the same dose

Primary: TSH-Oral drops

End point title	TSH-Oral drops[1]

End point description:

End point type	Primary

End point timeframe:

After 10±2 weeks of treatment

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This was a cross-over design

End point values	Tablets	T4 Oral drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	18		
Units: mIU/L				
arithmetic mean (standard deviation)	1.901 (± 0.957)	2.076 (± 1.334)		

Statistical analyses

Statistical analysis title	Paired samples t test
Comparison groups	Tablets v T4 Oral drops

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	ANOVA

Primary: TSH-T4 tablets

End point title	TSH-T4 tablets[2]

End point description:

End point type	Primary

End point timeframe:

After 10 ± 2 weeks of treatment

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This was a cross-over design

End point values	T4 Oral drops	T4 Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	21		
Units: mIU/L				
arithmetic mean (standard deviation)	1.901 (± 0.957)	1.759 (± 1.104)		

Statistical analyses

Statistical analysis title	Paired samples t test
Comparison groups	T4 Oral drops v T4 Tablets
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	ANOVA

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: Whole study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious AEs reported

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