Clinical Trial Protocol
Iranian Registry of Clinical Trials

09 Jun 2026

Formulation of Levothyroxine plus slow-release Liothyronine preparation for treatment of hypothyroidism (Clinical trial Phase 2& 3)

Protocol summary

Study aim

Phase 3: To assess and compare the efficacy of treatment with LT4+SR-T3 with that of LT4 monotherapy.

Design

The parallel randomized double-blind controlled clinical trial

Settings and conduct

Setting: Tehran Thyroid Study (TTS). At the first visit, a fasting blood sample will be obtained to measure serum TSH, TT3, TT4, FT4, FT3, FBS, lipid profile, insulin, HbA1C, HOMA-IR, SHBG, Enolase, LDH and CK, Ferritin, and metabolomics. Assessment of demographic data, quality of life, symptoms of thyroid function, and physical examination will be done. Body composition will be measured. The specified treatment will be given to both groups for 48 weeks. All tablets will be distributed in similar packages and the same size and color to ensure double-blinded design. Participants will be evaluated at baseline and 3 follow-ups at first, six, and 12 months after the start-up. All blood parameters and questionnaires will be filled out at baseline and 6 and 12 months after start-up. Also, the polymorphism related to deiodinase will be measured and compared between responders and non-responders.

Participants/Inclusion and exclusion criteria

Inclusion: Patients≥20y with hypothyroidism who attain euthyroidism under LT4 monotherapy. Exclusion: Pregnancy, end organ failure,cancer,taking methimazole,PTU,Tamoxifen, estrogen,progesterone and corticosteroids.

Intervention groups

Phase 3: 1. LT4+SR-T3 2. LT4 monotherapy

Main outcome variables

1. T3/T4 ratio,TSH,T4,T3, FT4,FT3 2. Clinical signs and symptoms of hypothyroidism 3. Quality of life 4. Patient preference 5. SerumLipid profile 6. FBS,HbA1C,HOMA-IR 7. SHBG 8. Enolase,LDH,CK 9. C-telopeptide or N-telopeptide 10. Ferritin 11. heart rate,BP 12. Metabolomics 13. Genetic polymorphism 14.Body composition

General information

Reason for update

Update 2: Reasons for the update The results of the clinical trial phase 2 were presented in a publication* and made us update the protocol of phase 3 in a few parts which are as follows: 1. We found that we should increase the ratio of SR-T3 to LT4 in the combination therapy. We also formulated SR-T3 in isolated tablets and not in one tablet/ capsule preparation due to the complexity of drug formulation and mixing a slow-release and normal-release product. In the new version, we consider treating hypothyroid patients with 75 µg lt4 and 15 µg sr-t3 and adjust the dosage based on the patient's weight. 2. We deleted the normal control group, there for our trial groups consist of one control group (LT4 monotherapy) and a trial group (receiving 75 µg LT4 and 15 µg SR-T3) 3. We decided to measure all outcomes in 6 and 12 months after starting the trial instead of only at the end of the trial. 4. We also decided to measure body composition as another outcome of the trial. *Mehran L, Amouzegar A, Foroutan SM, Masoumi S, Tohidi M, Abdi H, Aghaei A, Saghafinia AE, Azizi F. Pharmacodynamic and pharmacokinetic properties of the combined preparation of levothyroxine plus sustained- release liothyronine; a randomized controlled clinical trial. BMC Endocr Disord. 2023 Aug 28;23(1):182. UPDATE 1 The phase 3 clinical trial had been approved previously by IRCT, but due to Covid-19 epidemic crisis, the trial was postponed. At the present time, we are ready to conduct the trial, however, based on the recently published Consensus Statements to guide development of best-designed future clinical trials of LT4+LT3 combination therapy by the American Thyroid Association (ATA), British Thyroid Association (BTA), and European Thyroid Association (ETA), we are going to make some changes in the protocol and update the previous trial in some parts including the extension of follow- up period up to 12 months, adding new outcomes (bone markers of C-telopeptide/N-telopeptide,

Resting energy expenditure) and replacing the primary outcome to quality of life based on the suggestions made by the Consensus Statements1. Also, we added the complementary phase 2 clinical trial in a limited number of hypothyroid patients to evaluate the effectiveness and safety of monotherapy with our SR-T3 product. In the complementary phase 2 clinical trial we will select 30 patients with hypothyroidism (serum TSH>30 mU/L). These patients will be randomized into three groups receiving 1.6 µg/kg L-T4, equivalent doses of SRT3 and L-T3 of 0.55 µg/kg for 4 weeks and serum fT4, T3 and TSH will be measured weekly up to 4 weeks. This study is preliminary study to the previous approved clinical trial and the National Research Council of the Islamic Republic of Iran and the Human Research Review Committee of the Endocrine Research Center, Shahid Beheshti University, Tehran, Iran approved the complementary phase 2 protocol (IR.SBMU.ENDOCRINE.REC.1402.031). Trial participants will sign informed consent forms at baseline, and their personal information will remain strictly confidential. 1. Jonklaas J, Bianco AC, Cappola AR, Celi FS, Fliers E, Heuer H, McAninch EA, Moeller LC, Nygaard B, Sawka AM, Watt T, Dayan CM. Evidence-Based Use of Levothyroxine/Liothyronine Combinations in Treating Hypothyroidism: A Consensus Document. Thyroid. 2021 Feb;31(2):156-182.

Acronym

IRCT registration information

IRCT registration number: **IRCT20100922004794N12**
Registration date: **2020-02-27, 1398/12/08**
Registration timing: **prospective**

Last update: **2024-09-17, 1403/06/27**
Update count: **2**

Registration date

2020-02-27, 1398/12/08

Registrant information

Name
Fereidoun Azizi
Name of organization / entity
Country
Iran (Islamic Republic of)
Phone
+98 21 2240 9309
Email address
azizi@endocrine.ac.ir

Recruitment status

Recruitment complete

Funding source

Expected recruitment start date

2024-10-06, 1403/07/15

Expected recruitment end date

2025-10-23, 1404/08/01

Actual recruitment start date

empty

Actual recruitment end date

empty

Trial completion date

empty

Scientific title

Formulation of Levothyroxine plus slow-release Liothyronine preparation for treatment of hypothyroidism (Clinical trial Phase 2& 3)

Public title

Improvement in treatment of hypothyroidism using slow-release Liothyronine

Purpose

Treatment

Inclusion/Exclusion criteria

Inclusion criteria:

Inclusion criteria for Phase 2 and Phase 3 are the same as follows: Patients over 20 y. with hypothyroidism caused by any reason e.g. Hashimoto thyroiditis, treated Graves' patients after radioactive iodine intake, total thyroidectomized patients due to thyroid cancer or congenital hypothyroidism, who take LT4 monotherapy for at least 3 months and attain euthyroid status (TSH=0.5-5 mU/L is optimal).

Exclusion criteria:

Exclusion criteria for Phase 2 and Phase 3 are the same as follows: Pregnant women, those with end-organ failure e.g. chronic kidney and liver disease, congestive heart failure, or any kind of cancer, having other cofactors that mimicked symptoms of hypothyroidism, including low Hb, 25[OH] D deficiency, vitamin B12 deficiency, having long-standing psychiatric disorders(e.g major depressive disorders) and fibromyalgia, because those can mask some of the hypothyroid symptoms (eg, fatigue, arthralgia, depression, cognitive slowing); will be excluded. The patients should avoid taking methimazole, PTU, Tamoxifen, and drug-containing estrogen, progesterone, and corticosteroids.

Age

From **20 years** old to **75 years** old

Gender

Both

Phase

2-3

Groups that have been masked

- Participant
- Care provider
- Investigator
- Outcome assessor

Sample size

Target sample size: **100**

Randomization (investigator's opinion)

Randomized

Randomization description

Phase 3: Patients will be allocated to intervention and control groups using simple stratified randomization. 1. The groups with a daily intake of LT4+SR-T3 (Intervention Group) 2. The groups with LT4 mono-therapy (Control group) Participants will be randomized with equal probability (1:1) to receive one of the two treatments. As the size of each group is predicted to be 50 , the allocation sequence is generated with sample randomization and stratification by gender. The

sequences will be generated by the software and in Excel format. The patients sequentially entered to study based on this random sequence. Phase 2: After simple randomization, participants will be assigned to a pre-breakfast regimen of SRT3, L-T3, or L-T4 for 4 weeks. The dose of L-T4 is 1.6 µg/kg. This dosage will be adjusted to achieve 1:5 ratio of SR-T3 to LT4 in combination therapy. Patients will be recalled to the endocrine clinic for weekly follow-up visits and blood sampling.

Blinding (investigator's opinion)
Double blinded

Blinding description
After proper implementation of randomization, the subjects will be assigned to the groups using allocation concealment which helps to keep clinicians, participants and investigators unaware of upcoming assignments. The standard methods of ensuring allocation concealment will be sequentially numbered or coded opaque containers. For single-center clinical trials such as the current trial, we will identify a staff member not involved with the trial who can keep the randomization list. This staff will be instructed to keep the list private and to only reveal a treatment allocation after receiving information demonstrating that the patient is eligible and has consented to the trial. Both the subjects and the investigators will be kept from knowing who will be assigned to which treatment (double-blind) to fulfill this both groups will receive tablets that are identical in physical appearance, taste, and smell. The patients in the control group will receive Placebo instead of SR-T3.

Placebo
Not used

Assignment
Parallel

Other design features

Secondary Ids

empty

Ethics committees

1

Ethics committee

Name of ethics committee
National Institute for Medical Research Development

Street address
No. 21, Besat Ave, Chamran Highway, West Fatemi Ave.

City
Tehran

Province
Tehran

Postal code
1419693111

Approval date
2019-02-02, 1397/11/13

Ethics committee reference number
IR.NIMAD.REC.1398.007

2

Ethics committee

Name of ethics committee
Ethics Human Research Review Committee of the Research Institute for Endocrine Sciences, Shahid Behe

Street address
No. 24, Aarabi St. Velenjak area

City
Tehran

Province
Tehran

Postal code
1955858687

Approval date
2024-08-11, 1403/05/21

Ethics committee reference number
IR.SBMU.ENDOCRINE.REC.1403.061

Health conditions studied

1

Description of health condition studied
Hypothyroidism

ICD-10 code
E03.9

ICD-10 code description
Hypothyroidism, unspecified

Primary outcomes

1

Description
Quality of Life

Timepoint
At baseline and 6 and 12 months after trial

Method of measurement
Thyroid-specific Patient-Reported Outcome short-form (ThyPRO-39) modeled for hypothyroid subjects

Secondary outcomes

1

Description
SERUM TSH

Timepoint
At baseline and 3, 6, and 12 months after start-up

Method of measurement
on -20ºC stored serum samples by the electrochemiluminescence immunoasaay (ECLIA) method, using Roche Diagnostics kits and Roche/Hitachi Cobas e-411 analyzer (GmbH, Mannheim, Germany)

2

Description
Total T4, FREE T4, Total T3, T3/T4 ratio

Timepoint

At baseline and 3, 6, and 12 months after start-up

Method of measurement

electrochemiluminescence immunoasaay (ECLIA), Serum Total tri-iodothyronine(TT3), total thyroxine (TT4) will be determined on -20ºC stored serum samples by the electrochemiluminescence immunoasaay (ECLIA) method, using Roche Diagnostics kits and Roche/Hitachi Cobas e-411 analyzer (GmbH, Mannheim, Germany).

3

Description

clinical signs and symptoms of hypothyroidism

Timepoint

At baseline, 6 and 12 months after intervention

Method of measurement

thyroid symptom questionnaire

4

Description

Serum Lipid Profile(TG,HDL,LDL, TOTAL CHOLESTROL)

Timepoint

At baseline, 6 and 12 months after intervention

Method of measurement

Laboratory measurements with related kits

5

Description

FBS, Insulin sensitivity (HbA1C, HOMA-IR)

Timepoint

At baseline, 6 and 12 months after intervention

Method of measurement

Laboratory measurements with related kits

6

Description

Sex Hormone Binding Globulin (SHBG)

Timepoint

At baseline, 6 and 12 months after intervention

Method of measurement

Laboratory measurements with related kits

7

Description

Muscle thyroid status (Enolase, LDH and CK),

Timepoint

At baseline, 6 and 12 months after intervention

Method of measurement

Laboratory measurements with related kits

8

Description

Ferritin

Timepoint

At baseline, 6 and 12 months after intervention

Method of measurement

Laboratory measurements with related kits

9

Description

Metabolomics

Timepoint

At baseline, 6 and 12 months after intervention

Method of measurement

Laboratory measurements with related kits

10

Description

Cardiac parameters (resting heart rate, BP)

Timepoint

At baseline, 6 and 12 months after intervention

Method of measurement

With related measures

11

Description

Thr92Ala polymorphism of the type 2 deiodinase gene (DIO2) (Thr92Ala-DIO2) and polymorphisms in thyroid hormone transporters (e.g. MCT8, MCT10, OATP1C1)

Timepoint

at the end of the study

Method of measurement

whole genome sequencing

12

Description

Cognitive Function including memory and executive function

Timepoint

At baseline, 6 and 12 months after intervention

Method of measurement

with related tests

13

Description

C-telopeptide or N-telopeptide

Timepoint

At baseline, 6 and 12 months after intervention

Method of measurement

ECLIA

14

Description

Patient preference

Timepoint

At the end of trial

Method of measurement

With a question

15

Description

body composition and Resting Energy Expenditure (REE)

Timepoint

At baseline, 6 and 12 months after intervention

Method of measurement

Indirect calorymetry

Intervention groups

1

Description

Tavan Institute and Dorsa Pharmaceutical Company will formulate SR-T3 tablets (15 µg). Iran Hormone Company produces 50, 75, and 100 µg levothyroxine tablets. The patients will be randomly assigned to intervention (with a daily intake of LT4+SR-T3; 1:5 ratio) and control groups. The tablets should be taken in the morning at least half an hour before breakfast. At the first visit, a fasting blood sample will be obtained at 8 am and the specified treatment will be started on the same day. Participants will be evaluated at baseline and 3 consequent follow-ups (third, sixth, and 12 months after the start-up trial) up to 48 weeks. At each follow-up visit, venous blood samples will be collected from all participants after a 12-hour fast to measure serum TSH, total T3, total T4, free T4, and free T3. At the first and last visit total cholesterol, LDL, HDL, triglycerides, FBS, insulin, HbA1C, HOMA-IR, SHBG, Enolase, LDH and CK, Ferritin, C-telopeptide, N- N-telopeptide and metabolomics will be measured and heart rate, blood pressure will be evaluated. All questionnaires (Thyroid symptoms, Thypro-39 QOL) will be filled out at the first and last visits(6 and 12 months of start-up). The drug will be continued for 48 weeks. Patients will also be checked at 4 weeks intervals to measure TSH, assess adherence to therapy and adverse effects. Drug dosage would be adjusted to maintain serum TSH concentration within 0.5-5 mU/l.

Category

Treatment - Drugs

2

Description

Control group: The group with a daily intake of 100 µg LT4. The patients are advised to take tablets at least 0.5 hours before breakfast. At the first visit, a fasting blood sample will be obtained at 8 am and the specified treatment will be started on the same day. Participants will be evaluated at baseline and 3 consequent follow-ups (third, sixth, and 12 months after the start-up trial) up to 24 weeks. At each follow-up visit, venous blood samples will be collected from all participants after a 12-hour fast for measurement of serum TSH, total T3, total T4, free T4, and free T3. At the first and last visit total cholesterol, LDL, HDL and triglycerides, FBS, insulin, HbA1C, HOMA-IR, SHBG, Enolase, LDH, CK, Ferritin, C and N- telopeptides and metabolomics will be measured and heart rate and blood pressure will be evaluated. All questionnaires (Thyroid symptoms, and Thypro-39 QOL) will be filled out at first and last visits. The drug will be continued for 48 weeks. Patients will also be checked at 4 weeks intervals to measure TSH, assess adherence to therapy and adverse effects. Drug dosage would be adjusted to maintain serum TSH concentration within 0.5-3 mU/l.

Category

Treatment - Drugs

3

Description

Control group 2: There is also a normal age-sex matched control group which will not take any placebo, and they will only be evaluated for thyroid hormones, other biochemical and physical evaluations, and all questioners such as intervention groups at the first and last visits after 12 months.

Category

Treatment - Drugs

Recruitment centers

1

Recruitment center

Name of recruitment center

Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences

Full name of responsible person

Ladan Mehran

Street address

No.23, Erabi St, Yaman Ave., Velenjak

City

Tehran

Province

Tehran

Postal code

1985717413

Phone

+98 21 2243 2500

Fax

+98 21 2241 6264

Email

azizi@endocrine.ac.ir

2

Recruitment center

Name of recruitment center

Tehran Lipid and Glucose Study Unit

Full name of responsible person

Amir Abbas Momennan

Street address

No.80, Nahavandi St, Niroohavaiee Ave

City

Tehran

Province

Tehran

Postal code

1734893884

Phone

+98 21 7746 2215

Email

momenan_a@yahoo.com

Sponsors / Funding sources

1

Sponsor
Name of organization / entity
Dorsa Pharmaceutical Company
Full name of responsible person
Amir Esmail Saghafinia
Street address
No.1, Khajoo St, Rostamkhani St., Salehi Blvd., Tarasht
City
Tehran
Province
Tehran
Postal code
3188119978
Phone
+98 21 5461 2000
Fax
+98 21 6600 8533
Email
info@dorsadarou.com
Grant name
Grant code / Reference number
Is the source of funding the same sponsor organization/entity?
No
Title of funding source
Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences
Proportion provided by this source
90
Public or private sector
Private
Domestic or foreign origin
Domestic
Category of foreign source of funding
empty
Country of origin
Type of organization providing the funding
Industry

Person responsible for general inquiries

Contact
Name of organization / entity
Shahid Beheshti University of Medical Sciences
Full name of responsible person
Ladan Mehran
Position
Assistant Professor
Latest degree
Ph.D.
Other areas of specialty/work
Epidemiology
Street address
No.23, Erabi St, Yaman Ave., Velenjak
City
Tehran
Province
Tehran
Postal code
1985717413
Phone
+98 21 2243 2500
Email
lmehran@endocrine.ac.ir

Person responsible for scientific inquiries

Contact
Name of organization / entity
Shahid Beheshti University of Medical Sciences
Full name of responsible person
Fereidoun Azizi
Position
PROFESSOR
Latest degree
Subspecialist
Other areas of specialty/work
Internal Medicine
Street address
No.23, Erabi St, Yaman Ave., Velenjak
City
Tehran
Province
Tehran
Postal code
1985717413
Phone
+98 21 2243 2500
Email
azizi@endocrine.ac.ir

Person responsible for updating data

Contact
Name of organization / entity
Shahid Beheshti University of Medical Sciences
Full name of responsible person
Ladan Mehran
Position
Assistant Professor
Latest degree
Specialist
Other areas of specialty/work
Epidemiology
Street address
No.23, Erabi St, Yaman Ave., Velenjak
City
Tehran
Province
Tehran
Postal code
1985717413
Phone
+98 21 2243 2500
Email
lmehran@endocrine.ac.ir

Sharing plan

Deidentified Individual Participant Data Set (IPD)
No - There is not a plan to make this available

Justification/reason for indecision/not sharing IPD
These data are belonged to Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran

Study Protocol
No - There is not a plan to make this available

Statistical Analysis Plan
No - There is not a plan to make this available

Informed Consent Form
No - There is not a plan to make this available

Clinical Study Report
No - There is not a plan to make this available

Analytic Code
No - There is not a plan to make this available

Data Dictionary
No - There is not a plan to make this available