

# Clinical Trial Protocol

## Iranian Registry of Clinical Trials

15 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  $\geq 20$  years 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. Serum Lipid 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  $\mu$ g Lt4 and 15  $\mu$ g 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  $\mu$ g LT4 and 15  $\mu$ g 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 Statements<sup>1</sup>. 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)

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##### Email address

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#### 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 monotherapy (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 -20°C stored serum samples by the electrochemiluminescence immunoassay (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 immunoassay (ECLIA), Serum Total tri-iodothyronine(TT3), total thyroxine (TT4) will be determined on -20°C stored serum samples by the electrochemiluminescence immunoassay (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**

## 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 questionnaires 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

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### 2

#### Recruitment center

##### Name of recruitment center

Tehran Lipid and Glucose Study Unit

##### Full name of responsible person

Amir Abbas Momennan

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No.80, Nahavandi St, Niroohavaiee Ave

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## Sponsors / Funding sources

### 1

#### Sponsor

**Name of organization / entity**

Dorsa Pharmaceutical Company

**Full name of responsible person**

Amir Esmail Saghafinia

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No.1, Khajoo St, Rostamkhani St., Salehi Blvd.,  
Tarasht

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+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

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## Person responsible for scientific inquiries

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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

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## 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

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## **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