Clinical Trial Protocol
Iranian Registry of Clinical Trials

07 Nov 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

a single-center, two-arm, parallel-group, double-blind randomized controlled phase 3 trial with a target sample size of 100 participants. Participants in Phase 3 will be randomly allocated in a 1:1 ratio using a computer-generated random sequence to LT4+SR-T3 combination therapy or LT4 monotherapy .

Settings and conduct

Tehran Thyroid Study (TTS). Participants will be randomly assigned to LT4 monotherapy or LT4 plus SR-T3 and will receive treatment for 48 weeks. The LT4 group will receive matching SR-T3 placebo to maintain double blinding. At baseline, 6 months, and 12 months, clinical assessments, quality of life, thyroid-related symptoms, body composition, resting energy expenditure, and biochemical and thyroid hormone measurements will be performed. Cardiovascular safety will be evaluated by resting heart rate, blood pressure, and ECG. Patient treatment preference will be assessed at 6 and 12 months. Pharmacogenetic analyses will evaluate rs225014, rs12885300, rs225015, and rs17606253.

Participants/Inclusion and exclusion criteria

Inclusion criteria: Patients≥20y with hypothyroidism who attain euthyroidism under LT4 monotherapy. Exclusion criteria: 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

Quality of life (ThyPRO-39) TSH, TT3, TT4, FT3, FT4, T3/T4, T3/FT4, and FT3/FT4 Proportion of participants with T3/FT4 within the reference range Patient preference Serum lipid profile FBS, HbA1c, and HOMA-IR SHBG Enolase, LDH, CK C-telopeptide ،N-telopeptide Ferritin heart rate, blood pressure, ECG Metabolomics Pharmacogenetic variants Body composition, REE

General information

Reason for update

UPDATE NO. 3 Subject: Request for amendment and harmonization of completed clinical trial record — IRCT20100922004794N12 Dear IRCT Administration Team, We respectfully request amendment and harmonization of the record for the clinical trial IRCT20100922004794N12, entitled “Formulation of Levothyroxine plus slow-release Liothyronine preparation for treatment of hypothyroidism (Clinical trial Phase 2 & 3).” The Phase 3 component of this trial has now been completed. During preparation of the final Phase 3 manuscript, we performed a detailed reconciliation of the current IRCT record with the final Phase 3 protocol and identified several residual inconsistencies originating from earlier versions of the registration. We wish to emphasize that all substantive Phase 3 methodological decisions described in this amendment were made before recruitment of the first Phase 3 participant and before any Phase 3 outcome data were available. The present request is therefore intended to harmonize the public registry with the final pre-recruitment Phase 3 protocol and actual trial conduct; it does not represent changes made in response to study results. Secondary outcomes Serum TSH, total T3, total T4, FT3, FT4 and the derived T3/T4, T3/FT4, and FT3/FT4 ratios were prespecified secondary biochemical outcomes. The proportion of participants with a T3/FT4 ratio within the predefined reference range of 65–145 was also a prespecified secondary biochemical analysis and should be added to the registered outcomes. Phase 3 treatment groups The final Phase 3 trial consisted of two randomized parallel treatment groups: 1. LT4 monotherapy. 2. LT4 plus slow-release liothyronine. The previously planned age- and sex-matched euthyroid control group was removed before Phase 3 recruitment. Although this deletion is already mentioned in the IRCT update history, the previous normal-control description

remains in another section of the current registry. We respectfully request that this residual entry be removed or designated as superseded. Intervention and dose titration Participants allocated to combination treatment started therapy with LT4 plus SR-T3 at an initial SR-T3:LT4 dose ratio of approximately 1:5. The absolute starting doses were individualized according to each participant's thyroid hormone replacement requirement. The 1:5 ratio represented the initial treatment ratio and was not intended to remain fixed throughout follow-up. During the dose-adjustment period, LT4 and SR-T3 doses were individually titrated according to biochemical response, and consequently the SR-T3:LT4 dose ratio could change during follow-up. SR-T3 tablets containing 15, 20, and 25 µg were available for individual dose titration. LT4 tablets containing 50, 75, and 100 µg were also available. During the initial dose-adjustment phase, LT4 and SR-T3 doses were individually titrated according to biochemical response in order to maintain serum TSH within approximately 0.5–5.0 mU/L. In participants receiving combination treatment, the serum T3/FT4 ratio and the intended balance between LT4 and SR-T3 exposure were also considered during titration. We therefore request that the intervention section be revised to describe the starting regimen and subsequent individual titration rather than implying that the 1:5 ratio remained fixed throughout the study. LT4 monotherapy group Participants assigned to the control group received individualized LT4 replacement according to their pretrial replacement requirement and biochemical response, with dose adjustment when required to maintain euthyroidism. The control arm was not restricted to a fixed dose of 100 µg LT4 throughout follow-up. We therefore request correction of the registry section that currently describes a fixed 100-µg/day LT4 regimen. Placebo and masking Participants randomized to LT4 monotherapy received a matching placebo corresponding to SR-T3 in order to maintain double blinding. Active SR-T3 and placebo tablets were matched in physical appearance, taste, smell, and packaging. The current IRCT record contains an internal inconsistency in which the masking description correctly states that the control group received placebo instead of SR-T3, whereas another field states “Placebo: Not used.” We therefore request that the placebo field be corrected to indicate placebo used. Eligibility criteria The Phase 3 study included adults aged 20–75 years with hypothyroidism who were euthyroid on stable LT4 treatment before randomization. The final pre-recruitment exclusion criteria also included pregnancy or planned pregnancy and clinically important cardiovascular conditions, including unstable cardiovascular disease and cardiac arrhythmia. We additionally request clarification of the cancer-related eligibility wording so that the registry clearly distinguishes previous definitively treated thyroid cancer resulting in hypothyroidism from current or active malignancy, according to the final Phase 3 protocol. Follow-up period The Phase 3 intervention and follow-up period was 48 weeks, approximately 12 months, with principal assessments at baseline, 6 months, and 12 months and additional biochemical monitoring during the initial dose-adjustment period. We request correction of the isolated registry reference to “24 weeks,” which is inconsistent with the final Phase 3 protocol. Cardiovascular safety assessments Prespecified cardiovascular safety monitoring included resting heart rate, blood pressure, and serial electrocardiography. ECG variables included heart rate, RR interval, PR interval, QRS duration, QT interval, corrected QT interval, and clinically important rhythm and conduction abnormalities. ECG assessments were performed at baseline, 6 months, and 12 months. We request that these ECG assessments be added to the registered safety procedures and outcomes. Pharmacogenetic assessments The Phase 3 Pharmacogenetic analyses evaluated the candidate variants: rs225014, rs12885300, rs225015, and rs17606253. We request replacement of the current broad genetic description and reference to whole-genome sequencing with the actual candidate-variant analysis and laboratory methodology used in the study.The final laboratory method will be entered once all laboratory details have been confirmed: Patient preference Patient treatment preference was assessed during follow-up and at study completion. We request correction of the registered assessment timing where necessary. We therefore request completion of the following fields: Actual recruitment start date: 2024.12.03 Actual recruitment end date: 2024.12.08 Final participant/final study visit date: 2025.12.10 Post-trial treatment Following completion of assigned study treatment, participants were returned to conventional LT4 replacement therapy and followed until biochemical euthyroidism was re-established. We respectfully request that the above amendments be incorporated while preserving the original registration history and dates of previous protocol updates. The purpose of this amendment is to provide a complete, accurate, and transparent public record of the final Phase 3 protocol and actual study conduct. We again confirm that the substantive Phase 3 methodological decisions described above were established before Phase 3 recruitment began and before any Phase 3 outcome data were available. Please let us know if supporting documents, including dated protocol versions, ethics approvals, investigational-product documentation, or study records, are required.

Acronym

IRCT registration information

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

Last update: **2026-09-29, 1405/07/07**
Update count: **3**

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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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
2024-12-03, 1403/09/13
Actual recruitment end date
2024-12-08, 1403/09/18
Trial completion date
2025-12-10, 1404/09/19

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:
Adults aged 20 to 75 with hypothyroidism of any etiology who have been receiving stable levothyroxine (LT4) monotherapy for at least 3 months prior to randomization. Biochemically euthyroid patients, with serum TSH levels in the approximate range of 0.5 to 5.0 mIU/L. Eligible etiologies include, but are not limited to: Hashimoto's thyroiditis, Hypothyroidism following radioactive iodine treatment for Graves' disease, Hypothyroidism following definitive treatment for thyroid cancer. Prior treated thyroid cancer resulting in hypothyroidism is not considered an exclusion criterion, provided there is no current or active malignancy.
Exclusion criteria:
Pregnancy or planning for pregnancy during the study period; Clinically significant cardiovascular disease, including unstable cardiovascular disease, clinically significant cardiac arrhythmia, or congestive heart failure; Clinically significant renal or hepatic impairment; Current or active malignancy; Diseases or conditions that could significantly mimic the symptoms of hypothyroidism or confound their assessment, including anemia, vitamin D deficiency, vitamin B12 deficiency, chronic and clinically significant psychiatric disorders (such as major depressive disorder), and fibromyalgia. Additionally, patients taking methimazole, propylthiouracil, tamoxifen, estrogen- or progesterone-containing medications, or corticosteroids are excluded from the study.
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**
Actual sample size reached: **84**
Randomization (investigator's opinion)
Randomized
Randomization description
Phase 3: Participants will be randomly allocated in a 1:1 ratio to one of two parallel treatment groups: LT4 plus slow-release liothyronine (SR-T3) combination therapy (intervention group). LT4 monotherapy (control group). A computer-generated random allocation sequence will be prepared to assign participants to the two treatment groups with equal probability. The allocation sequence will be kept confidential, and participants will be enrolled sequentially according to the generated randomization sequence. Phase 2: After simple randomization, participants will be assigned to one of three pre-breakfast treatment regimens: SR-T3, L-T3, or L-T4, for 4 weeks. The L-T4 dose will be 1.6 µg/kg, and the corresponding SR-T3 and L-T3 doses will be administered according to the Phase 2 protocol. Participants will attend the endocrine clinic for weekly follow-up visits and blood sampling during the 4-week treatment period.
Blinding (investigator's opinion)
Double blinded
Blinding description
The random allocation sequence will be concealed from investigators and clinical staff involved in participant recruitment and assessment. The allocation sequence will be kept confidential by a designated staff member who will not be involved in participant recruitment, clinical management, or outcome assessment. After eligibility has been confirmed and written informed consent has been obtained, the participant will be assigned the next allocation code according to the randomization sequence. The treatment will be provided using the corresponding coded study medication without revealing the assigned treatment to participants or investigators. Both participants and investigators will remain blinded to treatment allocation. Participants assigned to the LT4 monotherapy group will receive a matching placebo corresponding to SR-T3. Active SR-T3 and placebo tablets will be matched in physical appearance, taste, smell, and packaging to maintain double blinding.
Placebo
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 Committee of the National Institute for Medical Research Development (NIMAD) of the Islamic R

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

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Province
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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, T3/FT4 and FT3/FT4 ratios and proportion of participants with T3/FT4 ratio whithin reference range

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 -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, ECG parameters)
Timepoint
At baseline, 6 and 12 months after intervention
Method of measurement
With related measures

11

Description
Pharmacogenetic variants: rs225014، rs12885300، rs225015، rs17606253.
Timepoint
at the end of the study
Method of measurement
genotyping

12

Description
C-telopeptide or N-telopeptide
Timepoint
At baseline, 6 and 12 months after intervention
Method of measurement
ECLIA

13

Description
Patient preference
Timepoint
At the end of trial
Method of measurement
With a question

14

Description
body composition and Resting Energy Expenditure (REE)
Timepoint
At baseline, 6 and 12 months after intervention
Method of measurement
Bioelectrical impedance analysis (BIA)

Intervention groups

1

Description
Participants randomized to combination therapy will start treatment with LT4 plus slow-release liothyronine (SR-T3) at an initial SR-T3:LT4 dose ratio of approximately 1:5. The absolute starting doses of LT4 and SR-T3 will be individualized according to each participant's thyroid hormone replacement requirement.The 1:5 ratio will represent the initial treatment ratio only and will not be required to remain fixed throughout follow-up. During the dose-adjustment period, LT4 and SR-T3 doses will be individually titrated according to biochemical response in order to maintain serum TSH within approximately 0.5–5.0 mU/L. In participants receiving combination therapy, the serum T3/FT4 ratio and the intended balance between LT4 and SR-T3 exposure will also be considered during dose titration. Consequently, the SR-T3:LT4 dose ratio may change during follow-up.SR-T3 tablets containing 15, 20, and 25 µg and LT4 tablets containing 50, 75, and 100 µg will be available for individualized dose adjustment. Study treatment will be administered once daily in the morning before breakfast and will continue for 48 weeks. After completion of study treatment, participants will return to conventional LT4 replacement and will be followed until biochemical euthyroidism is re-established.
Category
Treatment - Drugs

2

Description
Control group: LT4 monotherapyParticipants randomized to the control group will receive individualized LT4 monotherapy according to their pretrial LT4 replacement requirement and subsequent biochemical response. LT4 dosing will not be restricted to a fixed dose of 100 µg/day.LT4 tablets containing 50, 75, and 100 µg will be available for individualized dose adjustment. During follow-up, the LT4 dose will be adjusted when required to maintain biochemical euthyroidism, with serum TSH maintained within approximately 0.5–5.0

mU/L.Participants will take the assigned study tablets once daily in the morning before breakfast. Treatment will continue for 48 weeks. To maintain double blinding, participants in this group will also receive a matching placebo corresponding to SR-T3.

Category
Treatment - Other

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

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

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+98 21 2241 6264

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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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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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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
Associate Professor

Latest degree
Ph.D.

Other areas of specialty/work
Epidemiology

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Person responsible for scientific inquiries

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Position
PROFESSOR

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Subspecialist

Other areas of specialty/work
Internal Medicine

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Person responsible for updating data

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Full name of responsible person
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Assistant Professor

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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