Clinical Trial Protocol
Iranian Registry of Clinical Trials

07 Nov 2026

Evaluation of the Efficacy and Safety of Tirzepatide, a Dual glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide (GLP-1/GIP) Agonist, on Functional capacity in Reduced Ejection Fraction Heart Failure Patients with obesity: A Double-Blinded Randomized Controlled Trial

Protocol summary

Study aim

Evaluation of the Efficacy and Safety of Tirzepatide in Obese Patients with Heart Failure with Reduced Ejection Fraction

Design

A phase 3 randomized, parallel-group, triple-blinded, controlled clinical trial involving 60 patients, with randomization performed using the online software https://www.sealedenvelope.com

Settings and conduct

Study will be conducted at Masih Daneshvari, Shaheed Rajaei, Hazrat Rasoul Akram, and Tehran Heart Center hospitals. Patients with Heart Failure with Reduced Ejection Fraction less than or equal to 40% who have a BMI greater than or equal to 27 kilograms per square meter are enrolled. participants will be randomly allocated to the intervention and control groups using block randomization. The participants, investigators, healthcare personnel, and outcome assessors will be unaware of groups.

Participants/Inclusion and exclusion criteria

Inclusion criteria: Age greater than or equal to 18 years, Heart Failure with Reduced Ejection Fraction (HFrEF), and Body Mass Index (BMI) greater than 27 kilograms per square meter Exclusion criteria: Recent acute exacerbation of heart failure, uncontrolled blood pressure, advanced renal failure, hepatic dysfunction

Intervention groups

Participants in the intervention group will receive tirzepatide as subcutaneous injection using prefilled pens containing 2.5, 5, 7.5, and 10 milligram doses of tirzepatide manufactured by Sinagen (Spartina). Drug administration will be once weekly on a fixed day and time.Treatment will begin with a dose of 2.5 milligrams weekly and based on patient tolerance, will be gradually escalated every four weeks up to a maximum dose of 10 milligrams once weekly and continued until the end of the sixth month. The control group will receive placebo injections by identical pens manufactured by Sinagen, with the same administration schedule and conditions.

Main outcome variables

6-minute walk test distance

General information

Reason for update

Acronym

IRCT registration information

IRCT registration number: **IRCT20200209046427N3**
Registration date: **2026-06-22, 1405/04/01**
Registration timing: **prospective**

Last update: **2026-06-22, 1405/04/01**
Update count: **0**

Registration date

2026-06-22, 1405/04/01

Registrant information

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Name of organization / entity

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Recruitment status

recruiting

Funding source

Expected recruitment start date
2026-07-18, 1405/04/27
Expected recruitment end date
2027-06-11, 1406/03/21
Actual recruitment start date
empty
Actual recruitment end date
empty
Trial completion date
empty

Scientific title
Evaluation of the Efficacy and Safety of Tirzepatide, a Dual glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide (GLP-1/GIP) Agonist, on Functional capacity in Reduced Ejection Fraction Heart Failure Patients with obesity: A Double-Blinded Randomized Controlled Trial

Public title
Effect and Safety of Tirzepatide on Improving Functional Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Obesity
Purpose
Treatment
Inclusion/Exclusion criteria
Inclusion criteria:
Heart Failure with Reduced Ejection Fraction (HFrEF) with Ejection Fraction (EF) less than or equal to 40 percent based on recent echocardiography (performed within the previous 3 months) Body Mass Index (BMI) greater than or equal to 30 kilograms per square meter (kg/m²) BMI greater than or equal to 27 kg/m² and the presence of at least one obesity-related comorbidity, including hypertension, diabetes mellitus, or hyperlipidemia. Steady heart failure treatment for more than or equal to 4 weeks prior to enrollment (beta-blockers, renin–angiotensin system inhibitors/angiotensin receptor–neprilysin inhibitor (ARNI), and sodium-glucose cotransporter-2 (SGLT2) inhibitors if prescribed) Obtained Written informed consent
Exclusion criteria:
Acute heart failure decompensation within the past 4 weeks or recent cardiac hospitalization Uncontrolled blood pressure (Systolic Blood Pressure (SBP) less than 90 or greater than or equal to 180 millimeters of mercury (mmHg) Advanced renal failure (Estimated Glomerular Filtration Rate (eGFR) less than 30 milliliters per minute per 1.73 square meters) Severe hepatic impairment (Elevation of liver enzymes to three times the baseline level) Active pancreatitis History of medullary thyroid tumor or Multiple Endocrine Neoplasia Type 2 (MEN 2) in the patient or first-degree relatives Pregnancy or breastfeeding Known hypersensitivity to glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide (GLP-1/GIP) receptor agonists Concurrent use of weight-loss medications
Age
From **18 years** old
Gender
Both

Phase
3
Groups that have been masked

- Participant
- Care provider
- Investigator
- Outcome assessor
- Data and Safety Monitoring Board

Sample size
Target sample size: **60**
Randomization (investigator's opinion)
Randomized
Randomization description
The randomization method is based on block randomization, in which participants are equally allocated to the intervention and control groups. Participants are assigned in a 1:1 ratio (intervention to control) and enrolled in the study using random blocks of four generated by online software https://www.sealedenvelope.com. The investigators ensure the unpredictability of the allocation sequence and concealment of the allocation process using a computer-generated randomization procedure. In other words, through this centralized randomization method, the random allocation sequence remains concealed from the individuals enrolling participants into the study.
Blinding (investigator's opinion)
Triple blinded
Blinding description
The study is designed as a triple-blinded trial. In this study, participants, principal investigators, healthcare and research personnel responsible for patient care, data collectors, outcome assessors, and members of the Data Safety and Monitoring Board (DSMB) will be blinded to the allocation of participants to the intervention or control groups. The randomization and allocation process will be performed by an independent individual who is not involved in patient treatment, outcome assessment, or data analysis. Allocation codes will be kept in confidential sealed envelopes and will not be accessible to the research team, participants, or outcome assessors until completion of the final data analysis, except in emergency situations related to patient safety. Participants in the intervention group will receive tirzepatide, while participants in the control group will receive placebo. The placebo will contain all inactive ingredients and excipients of the active drug formulation except for the active ingredient tirzepatide. Placebo pens will be identical to the active drug pens in appearance, color, volume, odor, packaging, storage conditions, and method of administration. In addition, placebo pens will be prepared in visual dose presentations corresponding to 2.5, 5, 7.5, and 10 milligrams in order to maintain an identical dose-escalation process in both groups and prevent identification of treatment allocation. Administration of the active drug and placebo in both groups will be performed subcutaneously once weekly, on a fixed day and time, by a trained nurse. All participants in both groups will undergo identical administration procedures, follow-up visits, and outcome assessments in order to maintain blinding throughout all

stages of the study.

Placebo
Used

Assignment
Parallel

Other design features

Secondary Ids

empty

Ethics committees

1

Ethics committee

Name of ethics committee
Research Ethics Committees of National Research Institute of Tuberculosis and Lung Diseases - SBMU

Street address
Masih Daneshvari Tuberculosis and Pulmonary Diseases Research, Educational, and Medical Center, Shahid Beheshti University of Medical Sciences, Darabad Avenue, Shahid Bahonar roundabout

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Province
Tehran

Postal code
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Approval date
2026-04-29, 1405/02/09

Ethics committee reference number
IR.SBMU.NRITLD.REC.1405.005

Health conditions studied

1

Description of health condition studied
patients with reduced ejection fraction heart failure

ICD-10 code
I50

ICD-10 code description
Heart failure

2

Description of health condition studied
Overweight and obesity

ICD-10 code
E66

ICD-10 code description
Overweight and obesity

Primary outcomes

1

Description
Distance covered during the Six-Minute Walk Test (6MWT)

Timepoint
Before the intervention and 6 months after initiation of the intervention

Method of measurement
The Six-Minute Walk Test (6MWT) will be performed according to the standardized protocol of the American Thoracic Society (ATS) using a straight 30-meter corridor. Participants will be instructed to walk as far as possible at their maximum tolerated pace for six minutes and will be allowed to stop and rest if necessary. At the end of the test, the total distance walked will be recorded in meters. The 6MWT is a standardized, valid, and reproducible tool widely used for the assessment of functional capacity and exercise tolerance in patients with heart failure.

Secondary outcomes

1

Description
New York Heart Association (NYHA) functional class

Timepoint
Before the intervention and 6 months after initiation of the intervention

Method of measurement
According to the criteria of the New York Heart Association classification system.

2

Description
Fasting Blood Sugar

Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention

Method of measurement
Venous blood sampling after at least 8 hours of fasting and measurement of Fasting Blood Glucose using a standard laboratory assay kit based on the enzymatic glucose oxidase method.

3

Description
Glycated Hemoglobin (HbA1c)

Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention

Method of measurement
Biochemical assay kit for measurement of Glycated Hemoglobin

4

Description
Body Mass Index

Timepoint
Before the intervention and 6 months after initiation of the intervention

Method of measurement

Fixed stadiometer and weighing scale (Body Mass Index (BMI) equals weight in kilograms divided by height in square meters (kg/m²))

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Description
Quality of life
Timepoint
Before the intervention and 6 months after initiation of the intervention
Method of measurement
Score of Kansas City Cardiomyopathy Questionnaire

6

Description
Systolic blood pressure
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Measurement of Systolic Blood Pressure using a calibrated automatic blood pressure monitor after at least 5 minutes of rest in the seated position

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Description
Amylase
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Venous blood sampling and measurement of serum amylase using a standard laboratory assay kit based on the enzymatic colorimetric method.

8

Description
Alanine Aminotransferase (ALT)
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Venous blood sampling and measurement of serum Alanine Aminotransferase (ALT) using a standard laboratory assay kit based on the enzymatic spectrophotometric method.

9

Description
N-terminal pro–B-type Natriuretic Peptide (NT-proBNP)
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Human N-terminal pro–B-type Natriuretic Peptide (NT-proBNP) Enzyme-Linked Immunosorbent Assay (ELISA) Kit

10

Description
Total Cholesterol (TC)
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Venous blood sampling after at least 8 hours of fasting and measurement of serum Total Cholesterol (TC) using a standard laboratory assay kit based on the enzymatic colorimetric method.

11

Description
Ejection Fraction (EF)
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Echocardiography

12

Description
Gallbladder-related complications (cholelithiasis and cholecystitis)
Timepoint
At baseline (prior to initiation of the intervention), at the end of month 2, at the end of month 4, and at the end of month 6
Method of measurement
Blood tests and ultrasonography

13

Description
Injection-site reaction
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Physical Examination

14

Description
Hypoglycemia
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Standard laboratory assay kit for measurement of Blood Glucose using the enzymatic glucose oxidase method.

15

Description
Gastrointestinal adverse effects
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Interview and monitoring

16

Description
Pancreatitis
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Clinical assessment, standard laboratory assay kits for serum amylase and lipase measurement, and imaging studies when indicated.

17

Description
Tachycardia
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Physical examination, interview and monitoring

18

Description
diastolic blood pressure
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Measurement of diastolic Blood Pressure using a calibrated automatic blood pressure monitor after at least 5 minutes of rest in the seated position

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Description
Lipase
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Venous blood sampling and measurement of serum Lipase using a standard laboratory assay kit based on the enzymatic colorimetric method .

20

Description
Aspartate Aminotransferase (AST)
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Venous blood sampling and measurement of serum Aspartate Aminotransferase (AST) using a standard laboratory assay kit based on the enzymatic spectrophotometric method.

21

Description
Alkaline Phosphatase (ALP)
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Venous blood sampling and measurement of serum Alkaline Phosphatase (ALP) using a standard laboratory assay kit based on the enzymatic spectrophotometric method.

22

Description
Low-Density Lipoprotein (LDL)
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Venous blood sampling after at least 8 hours of fasting and measurement of serum Low-Density Lipoprotein (LDL) using a standard laboratory assay kit based on the enzymatic colorimetric method.

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Description
High-Density Lipoprotein (HDL)
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Venous blood sampling after at least 8 hours of fasting and measurement of serum High-Density Lipoprotein (HDL) using a standard laboratory assay kit based on the enzymatic colorimetric method.

24

Description
Triglycerides (TG)
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Venous blood sampling after at least 8 hours of fasting

and measurement of serum Triglycerides (TG) using a standard laboratory assay kit based on the enzymatic colorimetric method in the central laboratory of the study center.

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Description
Pulmonary Artery Pressure (PAP)
Timepoint
Before the intervention and at the end of the second month, the end of the fourth month, and the end of the sixth month after initiation of the intervention
Method of measurement
Echocardiography

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Description
Change in shared Molecular and Genetic Pathways Linking Obesity and Heart Failure with Reduced Ejection Fraction
Timepoint
Before the intervention and at the end of the sixth month after initiation of the intervention
Method of measurement
Venous blood sampling before the intervention and at the end of the study, extraction of ribonucleic acid from peripheral blood samples, and assessment of changes in the expression of genes involved in the shared molecular pathways of obesity and Heart Failure with Reduced Ejection Fraction using quantitative real-time polymerase chain reaction, next-generation sequencing techniques, and bioinformatics analysis.

Intervention groups

1

Description
Intervention group: Participants in the intervention group, in addition to receiving standard treatment for heart failure, will receive tirzepatide as a subcutaneous injectable pen. Tirzepatide is a dual agonist of glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide receptors. The study drug will be administered as prefilled injection pens containing doses of 2.5, 5, 7.5, and 10 milligrams manufactured by Sinagen (Spartina).Drug administration will be performed once weekly, on a fixed day and time, by a trained and experienced nurse at the treatment center. Subcutaneous injections will be administered in the abdomen, thigh, or upper arm, and the injection site will be rotated at each administration to reduce the risk of local adverse reactions.The initial tirzepatide dose will be 2.5 milligrams once weekly for four weeks. If tolerated without significant gastrointestinal adverse effects, the dose will be increased to 5 milligrams once weekly at week five. Thereafter, based on patient tolerance and clinical assessment, the dose will be gradually escalated up to a maximum dose of 10 milligrams once weekly and continued until the end of the sixth month. The dose will not exceed 10 milligrams per week.In the event of significant adverse effects or drug intolerance, the dose will be reduced to the last tolerated dose or treatment will be temporarily discontinued. All participants will be regularly monitored throughout the study for adverse effects, treatment adherence, and clinical response.
Category
Treatment - Drugs

2

Description
Control group: Participants in the control group, in addition to receiving standard treatment for heart failure, will receive placebo as a subcutaneous injectable pen. The placebo will consist of prefilled injection pens containing all inactive ingredients and excipients of the active drug formulation except for the active ingredient tirzepatide. The placebo pens will be identical to the active drug pens in appearance, color, volume, odor, packaging, and storage conditions and will be manufactured by Sinagen (Spartina) to prevent identification of treatment allocation by participants or study personnel. In addition, placebo pens will be prepared and packaged in dose presentations visually corresponding to 2.5, 5, 7.5, and 10 milligrams in order to maintain a dose-escalation process identical to the intervention group and preserve study blinding.Placebo administration will be performed once weekly, on a fixed day and time, by a trained and experienced nurse at the treatment center. Subcutaneous injections will be administered in the abdomen, thigh, or upper arm, and the injection site will be rotated at each administration to reduce the risk of local adverse reactions.Participants in the control group will receive placebo with the same administration schedule, frequency of injections, administration conditions, and dose-escalation pattern as the intervention group in order to maintain blinding throughout the study. The duration of intervention in the control group will also be six months. All participants in this group will be regularly monitored throughout the study for adverse effects, treatment adherence, and clinical status.
Category
Placebo

Recruitment centers

1

Recruitment center
Name of recruitment center
Masih Daneshvari Hospital
Full name of responsible person
Shadi Shafaghi
Street address
Masih Daneshvari Hospital, Darabad, Shahid Bahonar Street
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Email
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2

Recruitment center
Name of recruitment center
Tehran Heart Center
Full name of responsible person
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3

Recruitment center
Name of recruitment center
Rajaie Cardiovascular Medical and Research Center
Full name of responsible person
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4

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5

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Firoozgar Hospital, Beh Afarin Street, Karim Khan Zand Avenue, Valiasr Square, District 6, Tehran, Iran
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6

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7

Recruitment center
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Sponsors / Funding sources

1

Sponsor
Name of organization / entity
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Full name of responsible person
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7th Floor, Building No. 2, Shahid Beheshti University of Medical Sciences, Shahid Aarabi Street, Daneshjoo Boulevard, Velenjak, Tehran, Iran
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Grant name
Grant code / Reference number
Is the source of funding the same sponsor organization/entity?
Yes
Title of funding source
Shahid Beheshti University of Medical Sciences
Proportion provided by this source
100
Public or private sector
Public
Domestic or foreign origin
Domestic
Category of foreign source of funding
empty
Country of origin
Type of organization providing the funding
Academic

Person responsible for general inquiries

Contact
Name of organization / entity
Shahid Beheshti University of Medical Sciences
Full name of responsible person
Shadi Shafaghi
Position
MD, PhD, Faculty member-researcher
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Person responsible for updating data

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Sharing plan

Deidentified Individual Participant Data Set (IPD)
Yes - There is a plan to make this available
Study Protocol
Yes - There is a plan to make this available
Statistical Analysis Plan
Yes - There is a plan to make this available
Informed Consent Form
Yes - There is a plan to make this available
Clinical Study Report
Yes - There is a plan to make this available
Analytic Code
Yes - There is a plan to make this available
Data Dictionary
Yes - There is a plan to make this available
Title and more details about the data/document
All potentially shareable data will be available after de-identification of patient information.
When the data will become available and for how long
The access period starts after publication of the results
To whom data/document is available
Academic researchers will be granted access to the data upon providing an explanation for the need to access the information.
Under which criteria data/document could be used
Applicants are required to clearly explain the reason for requesting access to the data.
From where data/document is obtainable
Documents would be available according to cause of request from Dr Shadi Shafaghi Email: shafaghishadi@yahoo.com
What processes are involved for a request to access data/document
Applicants are required to submit a written request by email, including the reason for requesting access to the data. If approved, the requested information will be provided within a maximum of one week.
Comments