

# Clinical Trial Protocol

## Iranian Registry of Clinical Trials

31 May 2026

### **A phase III, randomized, multicenter, double-blind, two-armed, parallel, active-controlled, non-inferiority clinical trial to compare efficacy and safety of Evolocumab (CinnaGen) versus Evolocumab (Repatha®, Amgen Inc.) in patients with hyperlipidemia receiving concurrent high intensity statin**

#### **Protocol summary**

##### **Study aim**

To evaluate the efficacy and safety of Evolocumab (CinnaGen Co.) compared to Repatha® (Amgen Inc.) in patients with hyperlipidemia receiving concurrent high intensity statin

##### **Design**

Phase III, block-randomized, two-armed, double-blind, multi-center, parallel, active-controlled, non-inferiority clinical trial with 1:1 allocation.

##### **Settings and conduct**

Study place: Tehran (mentioned centers); population: hyperlipidemic and receiving concurrent high intensity statin; Blinded: double blind

##### **Participants/Inclusion and exclusion criteria**

Inclusion criteria: Individuals who are aged between 18 and 75 years; having signed a consent form; taking a stable daily dose of High intensity statin for at least four weeks prior to screening and have not achieved the target LDL-C level; are diagnosed with Established ASCVD or classified as very high risk in ASCVD assessment, fasting LDL-C  $\geq 70$  mg/dL, fasting triglycerides  $\leq 400$  mg/dL (4.5 mmol/L). Exclusion criteria: Heart failure of NYHA grade III or IV or LVEF  $< 30\%$ , uncontrolled blood pressure, Type 1 diabetes, newly diagnosed or uncontrolled Type 2 diabetes (HbA1c $>8.5\%$ ), active pancreatitis, serious uncontrolled cardiac arrhythmia, history of heart attack/unstable angina, PCI, CABG, stroke, deep vein thrombosis or pulmonary embolism  $\leq 3$  months before randomization, inadequate organ and marrow function, active infection, hepatitis C infection, administration of prohibited drugs and prohibited procedures within 3 months prior to randomization

##### **Intervention groups**

Intervention group: Evolocumab (Produced by CinnaGen Co.), 140 mg every two weeks, SC, Up to maximum 10 weeks (6 injections). Control group: Repatha® (Produced by CinnaGen Co.), 140 mg every two weeks, SC, Up to maximum 10 weeks (6 injections)

##### **Main outcome variables**

Percent change of LDL-C at week 12th compared to baseline

#### **General information**

##### **Reason for update**

To acceleration and optimization of the Clinical Trial recruitment and Execution processes, Dr. Hamidreza Hekmat and Dr. Ehsan Sekhavati Moghadam and Dr. Amir Sobh Rakhshan khah from Baharlou hospital and Dr. Hamed Vahidi from Imam Khomeini hospital and Dr. Mostafa Rouzitalab from Sina hospital have been added to the study.

##### **Acronym**

##### **IRCT registration information**

IRCT registration number: **IRCT20150303021315N32**  
Registration date: **2024-02-01, 1402/11/12**  
Registration timing: **prospective**

Last update: **2026-02-08, 1404/11/19**

Update count: **4**

##### **Registration date**

2024-02-01, 1402/11/12

##### **Registrant information**

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###### **Name of organization / entity**

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**Recruitment status**

**Recruitment complete**

**Funding source**

**Expected recruitment start date**

2024-04-20, 1403/02/01

**Expected recruitment end date**

2025-09-22, 1404/06/31

**Actual recruitment start date**

2024-07-02, 1403/04/12

**Actual recruitment end date**

2025-12-31, 1404/10/10

**Trial completion date**

empty

**Scientific title**

A phase III, randomized, multicenter, double-blind, two-armed, parallel, active-controlled, non-inferiority clinical trial to compare efficacy and safety of Evolocumab (CinnaGen) versus Evolocumab (Repatha®, Amgen Inc.) in patients with hyperlipidemia receiving concurrent high intensity statin

**Public title**

Evaluation of non-inferiority of efficacy and safety of Evolocumab (CinnaGen) versus Evolocumab (Repatha®, Amgen Inc.)

**Purpose**

Treatment

**Inclusion/Exclusion criteria**

**Inclusion criteria:**

Male or female  $\geq 18$  to  $\leq 75$  years of age Willingness for signing and having signed the informed consent form Should have received an approved high intensity statin at a stable daily dose, at least 4 weeks before screening, and has not achieved the target LDL-C level Having Established Atherosclerotic Cardiovascular Disease (ASCVD) (secondary prevention) or patients without established ASCVD (primary prevention) who are categorized as "very high risk" in ASCVD risk assessment according to AACE/ACE 2020 guideline ASCVD is defined as diagnosis of myocardial infarction, diagnosis of non-hemorrhagic stroke (TIA does not qualify as stroke for inclusion), symptomatic peripheral arterial disease (PAD), as evidenced by intermittent claudication with ankle-brachial index (ABI) greater than 0.85, or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease.- "Very high risk" in ASCVD risk assessment is defined as followed:• Diabetes with at least 1 risk factor(s)• CKD greater than or equal to 3 with albuminuria (assessed by urine albumin/urine creatinine ratio) • HeFH Fasting LDL-C as determined by the central laboratory at screening equal or greater than 70 milligram per deciliter Fasting triglycerides less than or equal to 400 milligram per deciliter

**Exclusion criteria:**

New York Heart Association (NYHA) III or IV heart failure

or LVEF less than 30% Uncontrolled hypertension (SBP more than 180 mmHg or DBP>110 mm Hg) Type 1 diabetes, newly diagnosed or poorly controlled type 2 diabetes (HbA1c more than 8.5%) Active pancreatitis Uncontrolled serious cardiac arrhythmia less or equal to 3 months prior to randomization History of myocardial infarction/unstable angina, PCI (percutaneous coronary intervention), CABG, or stroke less or equal 3 months prior to randomization Have inadequate organ and marrow function as indicated by laboratory values:• TSH less than LLN or TSH more than $1.5 \times$ ULN (in addition to abnormal free T4)• eGFR<30 mL/min/1.73m<sup>2</sup>• AST or ALT more than  $3 \times$ ULN• CK more than  $5 \times$ ULN Active infection Hepatitis C infection History of deep vein thrombosis or pulmonary embolism less or equal 3 months prior to randomization Administration of bile acid-sequestering resins, statins (outside of study regimen), ezetimibe, fibrates, less than 200 mg/day niacin, or more than 1000 milligram/day omega-3 fatty acids less or equal to 6 weeks prior to randomization Administration of cyclosporine, systemic steroids, vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions (except for the purpose of supplementation) less than 3 months prior to randomization Prohibited procedures such as cardiac surgery or revascularization, any weight loss procedure (e.g., bariatric surgery) within 3 months prior to randomization, or receiving any major organ transplant (e.g., lung, liver, heart, bone marrow and renal), LDL or plasma apheresis within 12 months prior to randomization Personal or family history of hereditary muscular disorders Major hematologic, metabolic, or GI disruption A female subject who is pregnant or breast feeding, or planning to become pregnant while enrolled in the study Previously received Evolocumab or any other investigational therapy to inhibit PCSK9 On a dietary regimen which is significantly deviated from recommended diet by physician (e.g., high levels of carbohydrates or lipids, low fiber regimens, or regular alcohol consumption) Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

**Age**

From **18 years** old to **75 years** old

**Gender**

Both

**Phase**

3

**Groups that have been masked**

- Participant
- Care provider
- Investigator
- Outcome assessor
- Data analyser

**Sample size**

Target sample size: **250**

Actual sample size reached: **250**

## Randomization (investigator's opinion)

Randomized

### Randomization description

The randomization plan of the patients will be carried out centrally using an R-CRAN software version 4.2.1. Using permuted block randomization, blocks (length of each block is 4 or 2) will be made, for a total of 250 patients (with 1:1 allocation ratio). Once the randomization will be made, each patient will be given a code with which she/he will be identified throughout the study. The assigned code will be made up of 3 numbers (corresponding to the randomization number) and by 4 initials (corresponding to the 2 first letters of the first name, the 2 first letters of the first surname) and 2 numbers (center code). The randomization number will be assigned in a consecutive way.

### Blinding (investigator's opinion)

Double blinded

### Blinding description

In general, both studied medications are diagnostically indistinguishable for both patients and medical staff, as they share identical physical characteristics in terms of shape, size, material, and color, rendering them visually indiscernible. The packaging for both formulations of Evolocumab is uniform to eliminate visual distinctions. Additionally, appropriate research labels are designed for the boxes and syringes of the studied medications, adhering to EMEA regulations. Both the brand and factory-produced medications are reliably manufactured and packaged in an identical manner. Specific coding on the medication labels links each medication to the respective patient, keeping patients, medical staff, and other personnel unaware of the type of administered medication. Information regarding patient groups and the type of medication administered is not disclosed to researchers, and sealed, Decoding packets are maintained securely by CRO representative. Furthermore, individuals conducting result preparation and data analyses remain unaware of patient group classifications.

### Placebo

Not used

### Assignment

Parallel

### Other design features

Group sample sizes of 125 and 125 achieve 80% power to detect non-inferiority using a one-sided, two-sample t-test. Efficacy of Repatha® in comparison with placebo for mean Percent change from baseline in LDL-C at week 12 in the reference study is reported 61.8. The margin of non-inferiority is 12.36%. The true difference between the means is assumed to be 0. The significance level (alpha) of the test is 0.025. The data are drawn from populations with standard deviations of 31.96. Considering a drop-out rate of about 15% total sample size required is 250 (125/125) patients

## Secondary Ids

empty

## Ethics committees

### 1

#### Ethics committee

##### Name of ethics committee

Iran University of Medical Sciences Ethics Committee

##### Street address

Iran University of Medical Sciences, Shahid Hemmat Highway

##### City

Tehran

##### Province

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##### Postal code

1449614535

#### Approval date

2023-12-13, 1402/09/22

#### Ethics committee reference number

IR.IUMS.REC.1402.797

## Health conditions studied

### 1

#### Description of health condition studied

Hyperlipidemia

#### ICD-10 code

E78.5

#### ICD-10 code description

Hyperlipidemia, unspecified

## Primary outcomes

### 1

#### Description

Outcome title: Percent change of LDL-C; This outcome is expressed in percentage (%) and is calculated from baseline to week 12, depicting the the percent change in LDL-C from study initiation to the end of the week 12.

#### Timepoint

Baseline, week 12

#### Method of measurement

Blood Biochemical Test

## Secondary outcomes

### 1

#### Description

Outcome title: Percent change of LDL-C; Relevant description: this outcome is expressed as a percentage (%) and it's calculation depends on week 10 and week 12 results. Initially, the mean LDL-C at weeks 10 and 12 will be calculated followed by the calculation of the percent change relative to the baseline. subsequently, a comparison will be made between the two groups.

#### Timepoint

Baseline, week 10, week 12

#### Method of measurement

Blood Biochemical Test

## 2

### **Description**

Outcome title: LDL-C Mean value change; Relevant description: this outcome is expressed as a value and it's calculation depends on week 10 and week 12 results. Initially, the mean LDL-C at weeks 10 and 12 will be calculated followed by the calculation of the change of the value relative to the baseline. subsequently, a comparison will be made between the two groups.

### **Timepoint**

Baseline, week 10, week 12

### **Method of measurement**

Blood Biochemical Test

## 3

### **Description**

Outcome title: LDL-C Value change; Relevant description: this outcome is expressed as a value and it's calculation depends on week 12 result. The change of the LDL-C value at 12th week relative to the baseline will be calculated. subsequently, a comparison will be made between the mean values of two groups.

### **Timepoint**

Baseline, week 12

### **Method of measurement**

Blood Biochemical Test

## 4

### **Description**

Percent change from baseline in triglycerides

### **Timepoint**

Baseline, week 12

### **Method of measurement**

Blood Biochemical Test

## 5

### **Description**

Percent change from baseline in HDL-C

### **Timepoint**

Baseline, week 12

### **Method of measurement**

Blood Biochemical Test

## 6

### **Description**

Percent change from baseline in total cholesterol at week 12

### **Timepoint**

Baseline, week 12

### **Method of measurement**

Blood Biochemical Test

## 7

### **Description**

Adverse events frequency

## **Timepoint**

Baseline and weeks 0, 2, 4, 6, 8, 10 and 12

## **Method of measurement**

Clinical monitoring

## 8

### **Description**

Immunogenicity: Anti-drug antibody

### **Timepoint**

Baseline, week 12

### **Method of measurement**

Enzyme-Linked Immunosorbent assay (ELISA)

## 9

### **Description**

Safety of laboratory tests

### **Timepoint**

Baseline, week 12

### **Method of measurement**

Blood Biochemical Test

## 10

### **Description**

Safety of vital sign

### **Timepoint**

Baseline, weeks 4, 8 and 12

### **Method of measurement**

Clinical monitoring

## **Intervention groups**

### 1

#### **Description**

Intervention group: Evolocumab (Produced by CinnaGen Co.), 140 mg every two weeks, sub cutaneous (SC), up to maximum 10 weeks (6 interventions)

#### **Category**

Treatment - Drugs

### 2

#### **Description**

Control group: Repatha® (Produced by CinnaGen Co.), 140 mg every two weeks, SC, up to maximum 10 weeks (6 interventions)

#### **Category**

Treatment - Drugs

## **Recruitment centers**

### 1

#### **Recruitment center**

##### **Name of recruitment center**

Dr. Seyed Hashem Sezavar Office

##### **Full name of responsible person**

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**2**

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**Sponsors / Funding sources****1****Sponsor****Name of organization / entity**

CinnaGen company

**Full name of responsible person**

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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**

CinnaGen company

**Proportion provided by this source**

100

**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

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**Latest degree**

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## Person responsible for updating data

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**Latest degree**

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**Other areas of specialty/work**

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## Sharing plan

**Deidentified Individual Participant Data Set (IPD)**

Undecided - It is not yet known if there will be a plan to make this available

**Study Protocol**

Undecided - It is not yet known if there will be a plan to make this available

**Statistical Analysis Plan**

Not applicable

**Informed Consent Form**

Undecided - It is not yet known if there will be a plan to make this available

**Clinical Study Report**

Undecided - It is not yet known if there will be a plan to make this available

**Analytic Code**

Undecided - It is not yet known if there will be a plan to make this available

**Data Dictionary**

Not applicable