Clinical Trial Protocol
Iranian Registry of Clinical Trials

04 Nov 2026

A Prospective Randomized Controlled Trial Comparing Three Advanced Therapies in the Treatment of Non-Alcoholic Steatohepatitis

Protocol summary

Study aim

To evaluate whether Sleeve Gastrectomy (SG) or medical therapies (GLP-1 agonist or SGLT-2 inhibitor) are more effective in improving liver histology (resolution of NASH and improvement of liver fibrosis) in patients with obesity, NASH, and fibrosis during 12-month follow-up.

Design

This is a parallel 3-arm randomized, controlled, pathologist-blinded, single center study. 105 patients are enrolled and followed for one year.

Settings and conduct

The study will be conducted in a tertiary center (Shariati hospital) by a collaborative effort between TUMS and IUMS from Iran. To evaluate the results of study, the end-of-treatment liver biopsies will be assessed by 3 blinded pathologists.

Participants/Inclusion and exclusion criteria

Inclusion Criteria: Male and female patients between the ages of 18 to 65 years old and a BMI between 30 – 45 kg/m2 with elevated LFT and abnormal elastography [score ≥8], which their NASH is confirmed in liver biopsy (presence of steatosis (>5%), hepatocyte ballooning, and lobular inflammation) [NAFLD Activity Score between 4 and 8, with at least 1 point from hepatocyte ballooning, plus presence of fibrosis stage F1, F2, or F3] Exclusion Criteria: Not having any of the above criteria or not accepting the inform consent, not being available during trial, history of any chronic disease (hepatic, renal, cardiopulmonary, ...), malignancies, immunodeficiency, major surgery, autoimmunity,...

Intervention groups

eligible patients with NASH and liver fibrosis will be randomized to one of the following treatments: • Liraglutide • Empagliflozin • Sleeve Gastrectomy At the end, the results will be assessed by baseline and end-of-treatment liver biopsies.

Main outcome variables

Significant improvement in histology in repeat biopsy: - Reduction in NAFLD Activity Score [3 points=<] - Resolution of hepatocellular ballooning - Improvement in fibrosis [1 point=<]

General information

Reason for update

A change in enrollment time due to the COVID-19 pandemic;

Acronym

SPLENDOR

IRCT registration information

IRCT registration number: **IRCT20200128046294N1**
Registration date: **2020-02-22, 1398/12/03**
Registration timing: **prospective**

Last update: **2021-06-14, 1400/03/24**
Update count: **2**

Registration date

2020-02-22, 1398/12/03

Registrant information

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Recruitment status

Recruitment complete

Funding source

Expected recruitment start date

2024-03-02, 1402/12/12

Expected recruitment end date

2026-03-03, 1404/12/12

Actual recruitment start date

empty

Actual recruitment end date

empty

Trial completion date

empty

Scientific title

A Prospective Randomized Controlled Trial Comparing Three Advanced Therapies in the Treatment of Non-Alcoholic Steatohepatitis

Public title

Sleeve Procedure vs Liraglutide vs Empagliflozin in NASH Disease and Obesity RCT (SPLENDOR)

Purpose

Treatment

Inclusion/Exclusion criteria

Inclusion criteria:

Is a candidate for general anesthesia Is eligible for bariatric surgery (SG) Is ≥18 and ≤65 years old Have a BMI ≥30 and ≤45 kg/m2 Have a platelet count >150,000 and International Normalized Ratio (INR) ≤1.2 Have appropriate composite entry criteria on liver biopsy: NAFLD with activity score between 4 and 8, presence of hepatocyte ballooning, and fibrosis stage between 1 and 3, confirmed by independent reviews by 3 liver pathologists. In case of any discrepancies in histopathologic report, a joint review by 3 study pathologists will be performed. Have the ability and willingness to participate in the study and agree to any of the arms involved in the study. Able to understand the options and to comply with the requirements of each arm. Have a negative urine pregnancy test at screening and randomization visits for women of childbearing potential. Women, of childbearing age, must agree to use reliable method of contraception for 1 year. 11. Patients with and without T2DM are eligible for the study. Patients with T2DM should have been on a stable dose of anti-diabetic medication for at least 3 months prior to entry, with HbA1c ≤8.5%. ALT & AST > 35 in female and 45 in male

Exclusion criteria:

1. Known history of other chronic liver diseases (drug induced, viral hepatitis, autoimmune, and genetic): a.Hepatitis B as detected by presence of hepatitis B surface antigen (HBsAg), b.Hepatitis C as detected by presence of hepatitis C virus (HCV) RNA, c.Autoimmune liver disease as diagnosed by antibodies and compatible liver histology, d.Primary biliary cirrhosis as defined by the presence of at least 2 criteria (elevated alkaline phosphatase, presence of anti-mitochondrial antibody, and histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts), e.Primary sclerosing cholangitis, f.Wilson's disease as diagnosed by low ceruloplasmin and compatible liver histology, g.Alpha-1-antitrypsin deficiency as diagnosed by alpha1-antitrypsin level and liver histology, h.Hemochromatosis as diagnosed by presence of 3+ or 4+ stainable iron on liver biopsy, i.Drug-induced liver disease as diagnosed by medical history, j.Known bile duct obstruction, k.Suspected or proven liver cancer Type 1 diabetes or autoimmune diabetes Known cases of human immunodeficiency virus infection Prior bariatric surgery of any kind Prior complex foregut surgery including any esophageal and gastric surgeries, anti-reflux procedures, splenectomy, biliary diversion, and trauma Thoracic, abdominal, pelvic and/or obstetric-gynecologic surgery within 6 months Any other surgery requiring general anesthesia within 6 weeks prior to signing the consent American Society of Anesthesiologists Class IV or V History of solid organ transplant Severe pulmonary disease defined as FEV1 < 50% of predicted value Cardiovascular conditions including significant known coronary artery disease, dysrhythmia, uncompensated congestive heart failure, history of stroke, or uncontrolled hypertension (defined as medically treated with the mean of 3 separate measurements systolic blood pressure > 180 mm Hg or diastolic blood pressure> 110 mm Hg) Chronic renal insufficiency with a eGFR is below 45 mL/min/1.73 m2, or being on dialysis Presence of moderate to severe GERD (Los Angeles classification B-D) Presence of moderate to large hiatal hernia (>3 cm) Presence of inflammatory bowel disease (Crohn's disease or ulcerative colitis) Psychiatric disorders including dementia, active psychosis, severe depression requiring > 2 medications, history of suicide attempts, active alcohol or substance abuse within the previous 12 months Pregnancy Breastfeeding Diagnosis of malignancy within three years (except squamous cell and basal cell cancer of the skin) Anemia defined as hemoglobin less than 9 g/dL Any medical condition requiring anticoagulation therapy that cannot be temporarily discontinued for surgical procedure Known history of clotting disorders, including pulmonary embolus and deep vein thrombosis Use of any medications (prescription or over the counter), including herbal or other supplements for treatment of obesity or liver conditions (e.g. vitamin E or pioglitazone) during the last 3 months Use of investigational therapy or participation in any other clinical trial within 3 months prior to signing the consent History of pancreatitis (acute or chronic) or pancreatic carcinoma History of thyroid cancer Presence of concerning thyroid nodule Family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 Liver biopsies < 5 mm in length Absence of hepatocyte ballooning on liver biopsy Absence of fibrosis on liver biopsy NAFLD Activity Score between 1-3 on liver biopsy Presence of fibrosis stage 4 (cirrhosis) Evidence of ascites, hepatic encephalopathy, portal hypertension, esophageal varices, splenomegaly, low platelet counts, or prolonged INR Current or history of substantial alcohol consumption (>20 g/day for women or >30 g/day for men, on average) for a period of more than 3 consecutive months within 1 year prior to screening Poor glycemic control (HbA1c >8.5%) Use of steroids (oral or intravenous), methotrexate, or Amiodarone (potential promoters of hepatic Steatosis) ALT or AST >300 U/L Recurrent major hypoglycemia or hypoglycemic unawareness Patients with >20 lbs weight gain or loss in last 6 months Inability to safely obtain a liver biopsy Any condition or major illness that, in the investigator's judgment, places the subject at undue risk by participating in the study Unable to understand the risks, benefits and compliance requirements of study Lack capacity to give informed

consent Plans to move outside the primary location of study (Tehran) within the next 12 months

Age

From **18 years** old to **65 years** old

Gender

Both

Phase

3

Groups that have been masked

- Outcome assessor

Sample size

Target sample size: **105**

Randomization (investigator's opinion)

Randomized

Randomization description

Patients will be randomized in a 1:1:1 ratio into one of the three treatment groups using computer generated randomization plan. The randomization will be stratified to ensure that there are equal numbers of patients with/without T2DM in each treatment group. Once eligibility is confirmed, the study coordinator will read the next letter in sequence to reveal the treatment assignment. Letters must be selected in sequence and not to be opened prior randomization. The date and time of randomization (reading letters) will be recorded.

Blinding (investigator's opinion)

Single blinded

Blinding description

Patients and investigators will not be blinded to treatment assignment. The treatment assignment will remain unknown until the patient is randomized after meeting all eligibility requirements. Pathologists who report the liver biopsies (to assess the primary and end-point results of study) are blinded to treatment assignment.

Placebo

Not used

Assignment

Parallel

Other design features

Secondary Ids

empty

Ethics committees

1

Ethics committee

Name of ethics committee

Ethics committee of Digestive Disease Research Institute - Tehran University of Medical Sciences

Street address

Digestive Disease Research Institute, Shariati Hospital, Kargar Street, Tehran

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Tehran

Province

Tehran

Postal code

1411713135

Approval date

2020-01-14, 1398/10/24

Ethics committee reference number

IR.TUMS.DDRI.REC.1398.007

Health conditions studied

1

Description of health condition studied

Nonalcoholic Steatohepatits (NASH)

ICD-10 code

K75.81

ICD-10 code description

Nonalcoholic steatohepatitis (NASH)

2

Description of health condition studied

Obesity

ICD-10 code

E66

ICD-10 code description

Overweight and obesity

Primary outcomes

1

Description

Liver Histopathology

Timepoint

before intervention and 12 months after intervention

Method of measurement

NAFLD activity score + hepatocellular ballooning + Fibrosis stage

Secondary outcomes

1

Description

Liver stiffness

Timepoint

before intervention and 12 months after intervention

Method of measurement

Fibroscan Score

2

Description

Liver Enzyme Activity

Timepoint

Before intervention and 6, 12 months after intervention

Method of measurement

Blood Test (ALT , AST , ALK.Phosphatase , Bilirubin)

3

Description

Anthropometric changes

Timepoint

Before intervention and 1, 3, 6, 9, 12 months after intervention

Method of measurement

Waist Circumference + Weight and BMI

4

Description

Metabolic Changes

Timepoint

Before intervention and 12 months after intervention

Method of measurement

Lab Lipid Profile (Chol, LDL, HDL, TG) + Blood Pressure (sphygmomonometer) + Lab (BS, HbA1C, HOMA-IR) + CRP

5

Description

Quality of Life

Timepoint

Before intervention and 6, 12 months after intervention

Method of measurement

SF-36 questionnaire + chronic liver disease questionnaire (CLDQ) for NASH (CLDQ-NASH)

6

Description

Complications

Timepoint

1, 3, 6, 9, 12 months after intervention

Method of measurement

Complications specifically related to NASH disease, as well as complications of liver biopsy, liraglutide, empagliflozin, and SG will be recorded and evaluated through history taking and physical examination.

Intervention groups

1

Description

Intervention group 1: Sleeve Gastrectomy - During laparoscopic SG, gastric resection starts within 3 to 6 cm of the pylorus along the greater curvature of stomach and ends with removal of the fundus, calibrated using a bougie.

Category

Treatment - Surgery

2

Description

Intervention group 2: Liraglutide - company: CinnaGen - prefilled multidose disposable pen with 18 mg liraglutide in 3 mL solution - dose: 1.8 mg once daily injection for 12 months - at any time of the day but at the same time each day - subcutaneous injection into the abdomen, thigh or upper arm

Category

Treatment - Drugs

3

Description

Intervention group 3: Empagliflozin Tablet - company: Abidi - dose: 10 mg once every day -

Category

Treatment - Drugs

Recruitment centers

1

Recruitment center

Name of recruitment center

Rasul-e Akram Hospital

Full name of responsible person

Dr Ali Kabir

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Rasul-e Akram Hospital, Niayesh Street, Sattarkhan Street, Tehran,

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2

Recruitment center

Name of recruitment center

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Full name of responsible person

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Sponsors / Funding sources

1

Sponsor

Name of organization / entity
Dr. Abidi Pharmaceuticals

Full name of responsible person
Dr. Abidi Pharmaceuticals

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https://www.abidipharma.com/

Grant name

Grant code / Reference number

Is the source of funding the same sponsor organization/entity?
Yes

Title of funding source
Dr. Abidi Pharmaceuticals

Proportion provided by this source
20

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

2

Sponsor

Name of organization / entity
CinnaGen

Full name of responsible person
CinnaGen

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No.2 , 7th St., Simaye Iran St., Shahrak Gharb, Tehran

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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

Proportion provided by this source
20

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

3

Sponsor

Name of organization / entity
Digestive Disease Research Institute

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
Digestive Disease Research Institute

Proportion provided by this source
30

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

Academic

4

Sponsor

Name of organization / entity
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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
Behbood Sanat Darman co

Proportion provided by this source
30

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
Tehran University of Medical Sciences

Full name of responsible person
Dr Anahita Sadeghi

Position
Assistant Professor

Latest degree
Subspecialist

Other areas of specialty/work
Gastroenterology

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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
Yes - There is a plan to make this available

Statistical Analysis Plan
Yes - There is a plan to make this available

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

Clinical Study Report
Not applicable

Analytic Code
Not applicable

Data Dictionary
Not applicable

Title and more details about the data/document
The Protocol and Statistical Analytic Plan (SAP) will be shared.

When the data will become available and for how long
At the time of publication

To whom data/document is available
Will be publically available as a supplement accompanying the published article.

Under which criteria data/document could be used
To interpret the findings of published study, and to use as a reference for future research

From where data/document is obtainable
On the website of journal that will publish the research

What processes are involved for a request to access data/document
The Protocol and Statistical Analytic Plan (SAP) will be publically available.

Comments