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Curcumin for non-alcoholic steatohepatitis (NASH)

Submission date	**Recruitment status**	[_] Prospectively registered
19/12/2021	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
21/12/2021	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
08/01/2024	Digestive System	[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Nonalcoholic steatohepatitis (NASH) is a leading cause of liver failure and cirrhosis in the world. There is no approved treatment for this disease.
Curcumin is a natural spice component that showed benefits in experimental models of NASH and improved surrogate markers of liver disease in humans, but its actual efficacy on liver histology, which is the main determinant factor of liver disease progression to cirrhosis, is unknown.

Who can participate?
Any adult patient with a biopsy-proven diagnosis of NASH, who is not involved in other experimental trials.

What does the study involve?
This study involves taking curcumin pills for 18 months and undertaking periodical office visits every 3 months. At the end of the treatment, liver biopsy will be repeated.

What are the possible benefits and risks of participating?
The possible benefits are the reversal of liver disease and the stop of progression to cirrhosis: the risks include allergic reactions to curcumin or to any component of the curcumin formulation and the risks associated with liver biopsy(pain, bleeding), which are very rare

Where is the study run from?
HUMANITAS Gradenigo hospital, Turin (Italy)

When is the study starting and how long is it expected to run for?
May 2018 to December 2022

Who is funding the study?
Indena S.p.A. (Italy), the manufacturer of this curcumin formulation, is funding the study

Who is the main contact?
Dr Giovanni Musso, Giovanni_musso@yahoo.it

Contact information

Type(s)
Principal investigator

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Dr Giovanni Musso

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Additional identifiers

Study information

Scientific Title
Safety and efficacy of phytosomial curcumin in non-alcoholic seatohepatitis (NASH): a double-blind, randomized, placebo-controlled trial

Study objectives
In patients with biopsy-proven nonalcoholic steatohepatitis (NASH), phytosomal curcumin for 18 months is safe, induces NASH resolution, and ameliorates histological features and NASH-associated cardiometabolic risk factors as compared with placebo.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 25/05/2018, A.O.U. San Luigi Gonzaga di Orbassano Ethics Committee (Azienda Ospedaliera Universitaria San Luigi Gonzaga, Regione Gonzole 10, 100043 Orbassano, Torino, Italy; +39 11-9026566
sperimentazioni@sanluigi.piemonte.it), ref: 0008942

Study design
Double-blind randomized placebo-controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Nonalcoholic steatohepatitis

Interventions
Pharmacological intervention (phytosomal curcumin) vs. placebo

Upon acceptance, patients will be randomly (computer-generated sequence) and double-blindly assigned to phytosomial curcumin 1 g twice daily or identical appearing placebo by mouth for 18 months. Both patient arms will be instructed to follow an intensive lifestyle program by an experienced dietician.
The following design will be applied:
-Randomization: computer-generated randomization table
-Double-blinding: pill containers coded with a similar number and with identical appearance. Pills will have identical appearance.
-Allocation concealment: the randomization table will be kept by the pharmacy where the pills have to be taken by the patients, so that only the pharmacist will know which intervention the patient will receive
-Stratification for: age decade, BMI range (normal weight, overweight, obese), sex, diabetes status (present/absent)
-Compliance assessment: pill count returned to the pharmacist

Periodical study visits: every 3 months all patients will undergo periodical check-up visits with individual interview, anthropometry, upper abdominal ultrasound and routine biochemistry.

End-of-treatment assessment: after 18 months of treatment, patients will repeat baseline assessment, including liver biopsy, oral glucose tolerance test, oral fat tolerance test, anthropometry upper abdomen ultrasound and biochemistry

Follow-up, end-of-study visit: 3 months after the end of treatment assessment, patients will undergo individual interview, anthropometry, upper abdominal ultrasound and routine biochemistry.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
phytosomal curcumin

Primary outcome(s)
Histological NASH resolution measured using the NASH Clinical Research Network criteria) after 72 weeks. Liver biopsies will be read and scored by a single pathologist (RP), who will be blinded to patient clinical characteristics and treatment allocation.

Key secondary outcome(s))
Current secondary outcome measures as of 17/06/2022:
1. A ≥1 stage improvement in NAFLD fibrosis stage and no worsening of NASH (with worsening defined as an increase of ≥1 point in either the lobular inflammation score or the hepatocyte ballooning score according to the NASH Clinical Research Network criteria) after 72 weeks

2. A ≥2-point improvement in NAFLD activity score (NAS), with at least 1 point improvement in either ballooning or lobular inflammation score according to the NASH Clinical Research Network criteria) after 72 weeks
3. Individual components of the NAFLD activity score (steatosis, hepatocyte ballooning, lobular inflammation) and the Kleiner fibrosis stage. Fibrosis stages 1a, 1b, and 1c were considered stage 1 for the purposes of analysis according to the NASH Clinical Research Network criteria) after 72 weeks
4. Changes from baseline to 48 weeks in serum liver enzyme concentrations, non-invasive biomarkers /scores of liver disease severity(including, but not limited to, cytokeratin 18 fragments, NAFLD fibrosis score, FIB-4), fasting lipid concentrations, glycaemic control (fasting plasma glucose, HbA1c), whole-body insulin resistance (fasting homoeostasis model of assessment of insulin resistance [HOMA-IR] and adipose tissue insulin resistance [ADIPO-IR]), anthropometric measures (body weight, BMI, waist circumference), physical activity and daily dietary consumption.
5. Safety endpoints included adverse events after the start of treatment, biochemical assessments, and clinical assessments. Selected events (including deaths, cardiovascular events, and acute pancreatitis) were adjudicated by an independent, external event-adjudication committee, whose members were unaware of the treatment assignments.
6. Change in estimated glomerular fuiltration rate (eGFR) at 18 months
7. Change in albuminuria measured using the albumin/creatinine ratio (ACR) at 18 months

Previous secondary outcome measures:
1. A ≥1 stage improvement in NAFLD fibrosis stage and no worsening of NASH (with worsening defined as an increase of ≥1 point in either the lobular inflammation score or the hepatocyte ballooning score according to the NASH Clinical Research Network criteria) after 72 weeks
2. A ≥2-point improvement in NAFLD activity score(NAS), with at least 1 point improvement in either ballooning or lobular inflammation score according to the NASH Clinical Research Network criteria) after 72 weeks
3. Individual components of the NAFLD activity score (steatosis, hepatocyte ballooning, lobular inflammation) and the Kleiner fibrosis stage. Fibrosis stages 1a, 1b, and 1c were considered stage 1 for the purposes of analysis according to the NASH Clinical Research Network criteria) after 72 weeks
4. Changes from baseline to 48 weeks in serum liver enzyme concentrations, non-invasive biomarkers /scores of liver disease severity(including, but not limited to, cytokeratin 18 fragments, NAFLD fibrosis score, FIB-4), fasting lipid concentrations, glycaemic control (fasting plasma glucose, HbA1c), whole-body insulin resistance (fasting homoeostasis model of assessment of insulin resistance [HOMA-IR] and adipose tissue insulin resistance [ADIPO-IR]), anthropometric measures (body weight, BMI, waist circumference), physical activity and daily dietary consumption.
5. Safety endpoints included adverse events after the start of treatment, biochemical assessments, and clinical assessments. Selected events (including deaths, cardiovascular events, and acute pancreatitis) were adjudicated by an independent, external event-adjudication committee, whose members were unaware of the treatment assignments.

Completion date
30/12/2022

Eligibility

Key inclusion criteria

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial except for protocol described pre-screening activities which require a separate informed
consent.
2. Male or female, aged 18-75 years (both inclusive) at the time of signing informed consent.
3. Histologic evidence of NASH based on experienced pathologist evaluation of a liver biopsy obtained up to 4 weeks before screening.
4. A histological NAS ≥ 4 with a score of 1 or more in each sub-component of the score based on pathologist evaluation.
5. NASH fibrosis stage 1, 2, or 3 according to the NASH CRN fibrosis staging system

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
75 years

Sex
All

Total final enrolment
52

Key exclusion criteria
1. Refusal or lacks capacity to give informed consent to participate in the trial.
2. Participation in any clinical trial of an investigational therapy or agent within 12 months of randomisation.
3. Patient (or carer) deemed not competent at using the correct site and technique for subcutaneous injection of the trial treatment (containing
dummy drug on practice).
4. NAFLD Activity Score (NAS) <3 on liver biopsy.
5. Child's B or C cirrhosis or clinical evidence of decompensated chronic liver disease: radiological or clinical evidence of ascites, current or previous hepatic
encephalopathy and evidence of portal hypertensive haemorrhage or varices on endoscopy.
6. Medical history of multiple drug allergies (defined as anaphylactoid drug reactions in >2 drug groups) or allegry to curry or curcumin-based nutraceuticals
7. Presence of any acute/chronic infections or illness that at the discretion of the chief investigator might compromise the patient's health
and safety in the trial.
8. Pregnancy or breastfeeding.

9. Women, of childbearing age, who are not willing to practise effective contraception (ie, barrier, oral contraceptives, impenon or past
medical history of hysterectomy) for the 48-week duration of the trial and for 1 month after the last administration of the drug.
10. Liver disease of other aetiologies (ie, drug-induced, viral hepatitis, autoimmune hepatitis, PBC, PSC, haemochromatosis, A1AT deficiency, Wilsons disease).
11. Average alcohol consumption >20 g/d(males) and >10 g/d(females) (as assessed by a validated questionnaire(AUDIT-10) within the last 5 years.
12. Medical/surgery history of; gastric bypass surgery, orthotopic liver transplant (OLT) or listed for OLT, hepatocellular, pancreatic, thyroid carcinoma, acute or chronic pancreatitis and total parenteral nutrition within 6 months of randomisation.
13. Diagnosis of malignancy within the last 3 years (with the exception of treated skin malignancies).
14. Hepatocellular carcinoma: dysplastic or intermediate nodules to be excluded. Regenerative and other nodules to be included at the discretion of the chief investigator.
15. Alanine aminotransferase or aspartate aminotransferase >10×upper limit of normal.
16. >5% weight loss since the diagnostic liver biopsy was obtained.
17. Recent (within 3 months of the diagnostic liver biopsy or screening visit) or significant change (as judged by the chief investigator) in dose of the following drugs: inducers of hepatic steatosis (steroids (oral/intravenous), methotrexate, amiodarone), orlistat and/or multivitamins/ vitamin E (containing >200% recommended daily amount; >30 mg/day).
18. Known positivity for antibody to HIV.
19. Currently being treated with renal replacement therapy (ie, haemodialysis or peritoneal dialysis).

Specific exclusion criteria for participants with T2D
1. Participants receiving thiazolidinediones (TZDs), dipeptidy peptidase (DPP) IV inhibitors and other GLP-1-based therapies.
3. HbA1c ≥10%.

Date of first enrolment
20/12/2021

Date of final enrolment
01/06/2022

Locations

Countries of recruitment
Italy

Study participating centre
HUMANITAS Gradenigo hospital
Corso Regina Margherita 8
Turin
Italy
10153

Study participating centre
Città della Salute Hospital
Dept of Medical Sciences
Corso Bramante 18
Turin
Italy
10124

Sponsor information

Organisation
Ospedale Humanitas Gradenigo

ROR
https://ror.org/017j6af40

Funder(s)

Funder type
Industry

Funder Name
Indena spa

Results and Publications

Individual participant data (IPD) sharing plan
Deidentified individual participant data will be made available upon reasonable request to the principal investigator via email (giovanni_musso@yahoo.it)

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file			07/09/2023	No	No