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A multicentre, randomised, double-blind placebo-controlled, phase II study to evaluate the safety, tolerability and dose of dried intestinal microbiota medicinal product EBX-102 in liver cirrhosis subjects (IMPuLCE)

Submission date
04/11/2022

Recruitment status
No longer recruiting

Registration date
23/08/2023

Overall study status
Ongoing

Last Edited
05/09/2023

Condition category
Digestive System

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English Summary
Background and study aims
The aim of the study is to assess the safety and tolerability of a potential treatment, called EBX-102, for patients with liver cirrhosis and to learn about the effects of EBX-102 on gut microbiota diversity. The main function of the liver is to remove toxins from the body, such as ammonia. In patients with cirrhosis, the build-up of ammonia can lead to significant illness which affects brain function and can lead to irreversible brain damage, coma or death. It has been shown that imbalanced gut microbial function plays a critical role in the development and worsening of cirrhosis. Patients with cirrhosis are also more susceptible to infections, are frequently prescribed antibiotics and have multiple hospitalisations. Current treatments such as lactulose and rifaximin help to eliminate ammonia from the body but there are side effects associated with their use. Medicinal approaches to correcting the gut imbalance are now of high interest to treat chronic liver cirrhosis and prevent the symptoms of raised ammonia levels, which can lead to hepatic encephalopathy (HE). EBX-102 has the potential to improve microbial diversity. EBX-102 capsules contain communities of dried, intestinal microorganisms from carefully screened pooled human stool samples. EBX-102 will be given as a single dose soon after randomisation under strict observation and thereafter participants are followed for 12 weeks to assess safety, tolerability and microbiota dynamics.

Who can participate?
Adults with liver cirrhosis

What does the study involve?
The study will involve two parts (A and B). At the end of Part A, a Dose Selection Review (DSR) meeting will occur to determine the dose for part B. Safety will be monitored by a Safety Review Team and assessments will include Documentation of adverse events, blood and urine tests, stool sample tests, ECG, HE assessments and questionnaires.

What are the possible benefits and risks of participating?
General risk: Most of the investigations carried out during the study are non-invasive and carry no risk.
Collecting blood samples from a vein in the arm: This can cause temporary discomfort, occasionally bruising/swelling and very rarely an infection at the site of puncture.
COVID-19 exposure: The study will follow the national guidance and local site policy in the management of the clinical study as appropriate with respect to COVID-19, to ensure the safety of the participants in relation to COVID-19 exposure. There is a low risk of transmission of an unwanted microorganism.
Possible side-effects:
Stomach pain and other gastro-type symptoms after taking the capsules.
The known side effects of this type of treatment typically include a rise in body temperature, bloating, diarrhoea and stomach cramps. These symptoms do not occur in everybody who takes them. Participants are encouraged to inform their study team about any side effects that they experience. The study doctor may provide additional medications to ease the experience of side effects, however, symptoms typically resolve within a few days.
There is a low risk of an infection caused by the transmission of an unwanted microorganism that may need to be treated with other medicines such as antibiotics.
The sponsor will provide compensation for any injury caused by taking part in this study in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI).

Where is the study run from?
NHS Greater Glasgow and Clyde (UK)

When is the study starting and how long is it expected to run for?
November 2022 to June 2025

Who is funding the study?
EnteroBiotix Limited (UK)

Who is the main contact?
Dr Ewan Forrest, Ewan.Forrest@ggc.scot.nhs.uk

Contact information

Type(s)
Principal Investigator

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Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1005961

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
EBX-102-102, IRAS 1005961, CPMS 53091

Study information

Scientific Title
A multicentre, randomised, double-blind placebo-controlled, phase II study to evaluate the safety, tolerability and dose of dried intestinal microbiota medicinal product EBX-102 in liver cirrhosis subjects (IMPuLCE)

Acronym
IMPuLCE

Study hypothesis
To assess the safety and tolerability of EBX-102 in liver cirrhosis subjects
To assess the effects of EBX-102 on intestinal microbiota diversity and associated factors

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 27/01/2023, East Midlands – Leicester South Research Ethics Committee (Equinox House, City Link , Nottingham, NG2 4LA, United Kingdom; +44 (0)207 104 8193 ; leicestersouth.rec@hra.nhs.uk), ref: 22/EM/0259

Study design
Multicentre randomized double-blind placebo-controlled phase II study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Condition
Liver cirrhosis and hepatic encephalopathy

Interventions
This is a phase II (first-in-human), multicentre, randomised, double-blind, placebo-controlled study.

Trial Arms: The study consists of two parts (A and B). Part A (Dose escalation) will involve two cohorts of approximately 12 subjects (n=24) with liver cirrhosis (MELD-Na score <12) without hepatic encephalopathy (HE) and who are not taking medications for Hepatic Encephalopathy (HE). Part B (Dose Expansion): Will involve approximately 32 subjects with liver cirrhosis (MELDNa score 12 -16), with or without minimal hepatic encephalopathy (MHE), and who are receiving treatment At the end of Part A, a Dose Selection Review (DSR) meeting will occur to determine the dose for part B.

Randomisation: Will be via IWRS. In Part A, in the first two cohorts, patients will be randomised at a ratio of 2:1 active: placebo) to assess the optimal dose regimen (n=24). Part B will consist of 32 subjects with a 5:3 randomisation active: placebo.

Dose/Dose Range/Frequency: EBX-102 will be given as a single dose, soon after randomisation under strict observation and thereafter participants are followed for 12 weeks to assess safety, tolerability and microbiota dynamics. The dose will depend on the part and cohort of the study the patient is randomised to.

Route of administration: Oral Administration

Intervention Type
Drug

Pharmaceutical study type(s)
Not Applicable

Phase
Phase II

Drug/device/biological/vaccine name(s)
EBX-102

Primary outcome measure
Safety and tolerability of EBX-102 measured using the incidence of adverse events, serious adverse events at week 12

Secondary outcome measures
Changes in intestinal microbiota taxonomic composition (bacterial diversity and relative abundance) measured using 16SrRNA sequencing of stool samples at week 1, week 4, week 8 and week 12 post-treatment

Overall study start date
01/11/2022

Overall study end date
30/06/2025

Eligibility

Participant inclusion criteria
1. Willing and able to provide informed consent
2. Male or female aged ≥18 years
3. A clinical diagnosis of LC, as confirmed by confirmatory scan (magnetic resonance imaging [MRI], 4. ultrasound, computed tomography [CT] or transient elastography) and/or needle biopsy of the liver. A needle biopsy is not a mandated procedure for study purposes.
5. (Part B only) Must be clinically stable on lactulose as deemed by the investigator for at least 1 month prior to randomisation, with the intent to remain on stable dose of treatment throughout the study period. Small daily variations of lactulose are permitted and must be recorded.
6. Subjects taking rifaximin should be stable at the prescribed dose for at least 4 weeks prior to randomisation.
7. MELD-Na score: 5.a - Part A: MELD-Na score of <12 5.b - Part B: Minimum MELD-Na score of 12 and a maximum MELD-Na score of 16.
8. Willing to abstain from consuming regular ‘over the counter’ pre or probiotics from pharmacies or other retailers from screening through to Week 12 after treatment.
9. Food products such as cheese, yoghurts, fermented pickles and probiotic drinks from the food section of supermarkets are acceptable.
10. Subjects with an alcohol use disorder should be willing to abstain from alcohol during the screening, treatment and follow up period.
11. Where subjects do not have an alcohol use disorder, alcohol may be consumed within the National Health Service (NHS) guidelines of ≤14 units per week, spread over at least 3 days per week.
12. Subjects with any other substance use disorder should be willing to abstain from those and other related substances, including substitutes, during the screening, treatment and follow up period.
13. Subjects with any substance or alcohol use disorder must have abstained from substance use for ≥3 months prior to screening. If women of child-bearing potential (WOCBP), subjects must

have a negative serum pregnancy test at screening and randomisation and must be willing to use a highly effective method of birth control for the duration of the study.
14. Acceptable methods of contraception:
14.1. Hormonal contraception associated with inhibition of ovulation
14.2. Intrauterine device (IUD)
14.3. Intrauterine hormone-releasing system (IUS)
14.4. Bilateral tubal occlusion
14.5. Vasectomised partner
14.6. Condom with spermicide
14.7. Sexual abstinence, in line with the preferred and usual lifestyle of the subject.
15. Periodic abstinence (such as calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
16. If male, subjects must be prepared to use reliable barrier method contraception and a second method such as spermicide for the duration of the study unless surgically sterile.
17. Willing and able to comply with all study requirements

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
60

Participant exclusion criteria
Subjects will be excluded from the study if they meet any of the following:
1. OHE as defined by Grade ≥2 WHG within 1 month of screening.
2. Part A only: any prior episode of HE
3. Overnight admission to hospital with OHE or any other liver-related complication, or any other non-elective admission to hospital, within the 4 weeks prior to screening.
4. Planned surgery requiring general anaesthetic during the course of the study.
5. History of total colectomy/ileostomy at any time, or bariatric/gastric surgery in the last 2 years.
6. Any other major intra-abdominal surgery within 60 days prior to screening
7. Confirmed diagnosis of Wernicke's Encephalopathy (WE) at any time prior to screening (prophylaxis of WE at any time prior to or during the study in accordance with the standard of care, with no confirmed diagnosis is permitted)
8. Korsakoff's Disease at any time prior to screening.
9. Confirmed diagnosis of dementia of any aetiology
10. Clinical signs and symptoms of dehydration at screening or baseline.
11. Any ongoing underlying issues which increase the risk of an OHE episode (e.g. unresolved gastrointestinal [GI] bleed; ongoing bacterial infection) at screening or baseline.
12. Diarrhoea of any aetiology within 7 days prior to screening.
13. Any anti-diarrhoeal or anti-peristaltic medication within 7 days prior to screening
14. Medications for HE

14.1. – Part A: medications for HE, including but not limited to lactulose, rifaximin, LOLA, BCAAs or other antibiotics. Rifaximin use for other conditions is also excluded.
14.2. – Part B: Part B: Medications for hepatic encephalopathy, including but not limited to: LOLA, BCAAs or antibiotics other than rifaximin within 3 months prior to screening. Lactulose is mandated.
15. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥4 x ULN
16. Planned organ transplant during the study period.
17. Chemotherapy, radiotherapy or immunotherapy within 3 months prior to baseline, or planned during the study
18. Life expectancy <4 months
19. Ongoing infectious hepatitis (A, B or C) or recent history that has not fully resolved at least 3 months prior to screening
20. Any other known immunodeficiency, including human immunodeficiency virus (HIV) with CD4+ T-cell counts <500 cells/mm3
21. Known gastrointestinal disease, including but not limited, to ulcerative colitis, Crohn's disease, coeliac disease, indeterminate colitis or microscopic colitis, diverticulitis, IBS.
22. Use of systemic antibiotics within 3 months prior to screening, or intended use during the study, with the exception of stable rifaximin for Part B subjects.
23. Patients receiving total parenteral or enteral nutrition. Nutritional supplements are permitted, with the exception of non-food pre- or probiotics.
24. Any autoimmune disease requiring, or that may require, systemic treatment with steroids and /or other immunosuppressants/immunomodulators and/or biological agents including SLE, RA, psoriatic arthritis and connective tissue disorders and MS. Autoimmune hepatitis is also excluded. Subjects with mild autoimmune disease not requiring systemic treatment, including vitiligo and alopecia areata, may be included.
25. Use of systemic steroids within the previous four weeks (inhaled and topical steroids are acceptable).
26. Uncontrolled Type I or Type II diabetes mellitus that has required hospitalisation within the last 3 months or, in the opinion of the investigator would lead to increased risk to the subject by study participation.
27. FMT within the past 12 months.
28. Subjects who are intoxicated at screening and/or randomisation.
29. Any ongoing alcohol or substance dependency within 3 months of screening.
30. Prior substance misuse requiring current substitute, e.g. Methadone within 1 month of screening.
31. Use of opiates for any reason within 1 month of screening.
32. Previous anaphylactic reaction to any substance, or allergies requiring the subject to carry an epinephrine autoinjector.
33. Subjects with dysphagia, or inability to swallow up to 10 size 0 capsules in a single sitting (30 minute period), or inability to ingest capsules (e.g. severe nausea, vomiting, delayed gastric emptying) or history of 'choking' on capsules.
34. Any condition for which, in the opinion of the investigator, the treatment or participation in the study may pose a health risk to the subject
35. Planned or active participation in any other study with an investigational medicinal product (IMP).
36. Have taken an IMP within the last 3 months.
37. COVID-19 infection requiring hospital admission with overnight stay within 1 month prior to screening.

Recruitment start date
04/05/2023

Recruitment end date
04/04/2024

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Glasgow Royal Infirmary
84 Castle Street
Glasgow
United Kingdom
G4 0SF

Study participating centre
King's College Hospital NHS Foundation Trust
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Aberdeen Royal Infirmary
Foresterhill Road
Aberdeen
United Kingdom
AB25 2ZN

Study participating centre
North Tyneside General Hospital
Rake Lane
North Shields
United Kingdom
NE29 8NH

Study participating centre

Nottingham University Hospitals NHS Trust - Queen's Medical Centre Campus
Nottingham University Hospital
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Hull University Teaching Hospitals NHS Trust
Hull Royal Infirmary
Anlaby Road
Hull
United Kingdom
HU3 2JZ

Study participating centre
Queen Elizabeth University Hospital
1345 Govan Road
Glasgow
United Kingdom
G51 4TF

Study participating centre
Bradford Teaching Hospitals NHS Foundation Trust
Bradford Royal Infirmary
Duckworth Lane
Bradford
United Kingdom
BD9 6RJ

Study participating centre
University Hospitals of Leicester NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
University Hospital Southampton NHS Foundation Trust
Southampton General Hospital

Tremona Road
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SO16 6YD

Study participating centre
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Sponsor type
Industry

Website
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Funder(s)

Funder type
Industry

Funder Name
EnteroBiotix Limited

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Internal report
3. Conference presentation
4. Publication on website
5. Other publication

Following the completion of the study, the results will be reported publicly. The results of the study will be available after it finishes and will be published in a medical journal and/or presented at a scientific conference. The data will be anonymous and none of the participants involved in the study will be identified in any report or publication. This study will be automatically registered at the ISRCTN Registry. This website will include a summary of the results.

Intention to publish date
30/06/2026

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Julie Bakobaki, j.bakobaki@enterobiotix.com

IPD sharing plan summary
Available on request