Safety and Viability of an E. coli Nissle Colibactin Knockout in Healthy Volunteers: A Randomised Controlled Safety Study

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Assess the safety and tolerability of the EcNΔClbP strain relative to the EcN wildtype strain following a 1-week daily administration, through questionnaires, medical examination and measurement of inflammatory markers.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON53774

Source
ToetsingOnline

Brief title
SECONI

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Gastrointestinal conditions NEC

Synonym
diabetes, Diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: NNF-CAMIT-research foundation;een onafhankelijke grote wetenschappelijke stichting uit Denemarken die het onderzoek sponsort

Intervention

Keyword: Advanced Microbiome Therapeutics, E coli Nissle 1917, E coli Nissle 1917 colibactin knockout

Outcome measures

Primary outcome

Primary outcome is the number, duration and severity of adverse reactions to assess the safety/tolerability of the EcNΔClbP strain compared to the wild type strain. In addition, changes in inflammatory markers (CRP, leukocytes) will be measured as well as blood safety parameters (liver and renal function, complete blood count, lipids and glucose/insulin) at V2, V3 and V4. Finally, quality of life, gastrointestinal (GI) comfort and stool metrics are recorded through validated questionnaires (gastro-intestinal quality of life, GIQLI, and Bristol Stool Chart) at V2, V3 and V4.

Secondary outcome

Secondary outcomes include:

- Quantific ation of EcN in faeces samples collected throughout the two weeks via qPCR to assess engraftment, viability and washout of the EcN.

- (Anaerobic) culturing of fresh faeces samples (V2, V3 and V4) on EcN selective media to assess engraftment, viability and washout of the EcN.

- Staining of EcN ribosomal RNA to assess engraftment, viability and washout of the EcN.

- Metagenomic sequencing will be performed on faecal samples from V2, V3 and V4 to study the effect of the intervention on the gut microbiota composition and to mathematically assess the growth/engraftment of the EcN in situ (peak-to-trough ratio). In addition, the effect of gut microbiota composition on engraftment of both EcN strains will be assessed.

Other study parameters include:

- Changes in glucose metabolism, measured by CGM (freestyle libre) during the week before intervention and two weeks thereafter.
- Changes in 24h faecal and fasting plasma bile acids and SCFA will be measured at V2, V3 and V4.
- Bristol Stool Chart score at V2, V3 and V4
- Physical parameters (length, weight, blood pressure, body impedance analysis) at V2, V3 and V4
- Dietary intake during the week prior to the intervention and the two-week study period.

Study description

Background summary

E. coli Nissle 1917 (EcN) is a well-established, safe human probiotic. Over the past years, many bioengineering strategies for this strain have been developed and functionally enhanced E. coli Nissle strains have been used in several clinical trials. However, it has been shown that EcN harbors a cluster of genes coding for the biosynthesis of hybrid nonribosomal peptide-polyketide(s), so-called pks-islands, ultimately leading to the

production of colibactin. St udies have shown that colibactin causes cell cycle arrest, DNA double-strand breaks, and senescence in mammalian cells. Moreover, colibactin-producing E. coli accelerate tumor progression in multiple mouse models. To create a safe platform strain for future advanced microbiome therapeutics (AMT) development, the colibactin peptidase (ClbP) gene has been removed from EcN. In mice models, safety of this EcN colibactin knockout (EcNΔClbP) has been shown, as well as a reduced capacity to colonise the gut, which can be beneficial in therapeutic settings . To assess the safety of the EcNΔClbP strain in humans and compare its kinetics compared to the wildtype EcN, we here propose a randomised controlled safety study in healthy volunteers.

Study objective

Assess the safety and tolerability of the EcNΔClbP strain relative to the EcN wildtype strain following a 1-week daily administration, through questionnaires, medical examination and measurement of inflammatory markers.

Study design

Double-blind, randomised, controlled, safety study.

To study the above objectives, a double-blind randomised controlled intervention study will be performed within the department of Internal and Vascular Medicine of the Amsterdam UMC, location AMC. The complete study duration is 2 weeks (1 week of intervention, followed by 1 week of follow-up). During this period, subjects are requested to visit the AMC 3 times (and once for the screening). A more detailed overview of the study visits can be found below, followed by a schematic overview of the study design (Figure 1).
3.2 Study visits
Subjects will visit the AMC four times in total. Each visit will take 30-60 minutes (maximum of 4 hours over 2 weeks). A more detailed description of all measurements and procedures can be found in section 7.3 Study procedures.

Visit 1: screening
During the first visit, oral and written information on the study will be given to the participant after which informed consent will be obtained. Thereafter, subjects will be screened for eligibility through examination of their medical history, a physical examination and analysis of blood safety parameters. After inclusion, subjects will receive the necessary material and instructions regarding the faeces collection and the nutritional diary. Before visit 2, subjects will be randomly assigned to either the EcNΔClbP strain or the wildtype EcN strain. One week before visit 2, subjects will start wearing the CGM device, collect a faeces sample and start recording their dietary habits using an online dietary booklet (https://mijn.voedingscentrum.nl/nl/eetmeter).

Visit 2: baseline visit
Within 3 months of the screening, subjects will come fasted to the AMC, bringing the 24h faeces and a fresh faecal sample with them. These will be stored at -80° C until analysis. During the visit, subjects will undergo a physical examination (length, weight, blood pressure, body impedance analysis) and fasting venous blood will be drawn. Subjects will complete questionnaires on the Bristol stool chart and GI comfort, dietary habits/eating behaviour and QoL questionnaires, after which they receive the allocated study intervention. Subjects will ingest the EcN study product daily around the same time for 7 days. Subjects are asked to collect faecal samples, wear a CGM device and to record their dietary habits over the next 14 days using an online dietary booklet (https://mijn.voedingscentrum.nl/nl/eetmeter).

Visit 3: intervention visit
After one week, subjects will come fasted to the AMC, bringing the 24h faeces and a fresh faecal sample with them and any unused EcN study product. The same measurements and questionnaires from visit 2 will be repeated. There will be special attention for clinically relevant (serious) adverse events ((S)AE). This will be the last day of the study intervention, which is followed by a one-week washout period.

Visit 4: follow-up visit
After one week, subjects will come fasted to the AMC, bringing the 24h faeces and a fresh faecal sample with them. The same measurements and questionnaires as during visit 2 and 3 will be repeated and again, there will be special attention for clinically relevant (serious) adverse events ((S)AE). This is the last study visit.

Intervention

The investigational products are the EcNΔClbP strain and the active comparator is the wildtype EcN strain. The wildtype EcN strain is a well-established, safe human probiotic and has been used for over a century [3]. Participants will be randomised to the intervention or control group in CASTOR. Subjects in the intervention group will receive 1011 CFU of the EcNΔClbP strain daily for 7 days. In the control group, subjects will receive 1011 CFU of the wildtype EcN strain daily for 7 days. Both strains will be produced under HACCP guidelines by NIZO, Ede, the Netherlands

Study burden and risks

Subjects will visit the AMC (fasted) four times (30-60 min per visit): visit 1 = screening; visit 2 = baseline measurements + start intervention; visit 3 = follow-up at week 1; visit 4 = follow-up at week 2. During these visits a physical examination will be performed, questionnaires will be filled out and blood is drawn, 14-32 ml per visit (110 ml in total). In addition, subjects

will be asked to collect faeces at home, wear a CGM device during the study and keep a food diary during 2 weeks. Subjects will receive ¤200 as compensation for their participation as well as reimbursement of their travel expenses.
The risks associated with participation can be considered negligible. The potential side-effects of the EcNΔClbP strain are expected to be equal or less prominent compared to the wildtype EcN. The wildtype EcN strain is a well-established, safe human probiotic and has been used for over a century. The most common side effect that has been reported is flatulence after initiation of treatment, whereas abdominal pain, gut noises, loose stools, diarrhoea, nausea and vomiting may very rarely occur. The amount of blood drawn is below the maximum 500 mL per day; other study procedures are considered harmless and will not cause any physical or psychological discomfort.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Healthy male or female of Caucasian descent
o If female, postmenopausal
- Age: 18-65 years old
- BMI: 18-25 kg/m2
- Subjects should be able to give informed consent

Exclusion criteria

- Use of any systemic medication (except for paracetamol), including proton pump inhibitors, antibiotics and pro-/prebiotics in the past three months or during the study period.
- Use of the EcN probiotic strain (Mutaflor®) in the past 12 months.
- (Expected) prolonged comprised immunity (e.g. due to recent cytotoxic chemotherapy or human immunodeficiency viruses (HIV) infection with a CD4 count < 240/mm3).
- History of moderate to severe disease of the digestive tract, such as celiac disease, chronic diarrhoea (>=3 stools/day for >4 weeks), chronic obstipation (<2 defecations/week for >3 months), Irritable Bowel Syndrome (IBS) (according to Rome IV criteria) or Inflammatory Bowel Disease (IBD).
- Any gastro-intestinal disorder within the past 6 months
- Smoking or illicit drug use (e.g. MDMA/amphetamine/cocaine/heroin/GHB) in the past three months or use during the study period.
- Use of >21 units of alcohol per week on average in the past three months or use of >2 units of alcohol during the study period.
- Pregnancy or breast feeding
- Simultaneous participation in other studies

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-09-2023
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	07-03-2023
Application type:	First submission
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL83158.018.22