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BEN8744 - First doses in humans

Submission date 06/06/2023	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 14/06/2023	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 09/04/2026	**Condition category** Digestive System	[_] Individual participant data

Plain English summary of protocol

Background and study aims
BEN8744 (the study medicine) is an experimental new medicine for treating inflammatory bowel diseases such as ulcerative colitis (UC). UC patients have problems with their immune system which causes their intestines to become inflamed, leading to symptoms such as frequent diarrhoea, stomach aches, and incontinence (difficulty controlling when they go to the toilet). It is hoped that BEN8744 will work by blocking the activity of an enzyme (a substance in the body that breaks down other substances) called PDE10A that's involved in UC. We think BEN8744 will be safer and more effective than current treatments for UC, which aren't very reliable, work too slowly, or cause bad side effects.

We'll test single and repeated doses of BEN8744 or placebo (a dummy medicine that looks the same as the study medicine but has no active ingredient) by mouth. BEN8744 has never been given to humans before, so we'll start with a small dose and increase the dose as the study progresses. We aim to find out its side effects and blood levels when taken by mouth and whether food affects the blood levels.

Who can participate?
Healthy men and women, aged 18-65 years

What does the study involve?
This is a 3-part study (Parts A, B and C) in up to 108 healthy people, aged 18-65 years

In Part A, we'll give up to 64 participants single doses of BEN8744 or placebo. They'll take about 2 weeks to finish the study, stay on the ward for 4 nights and 5 days in a row and make 2 outpatient visits.

In Part B, we'll give up to 12 participants single doses of BEN8744 with and without food. They'll take up to 3 weeks to finish the study, stay on the ward for 4 nights and 5 days in a row on 2 occasions, and make 2 outpatient visits.

In Part C, we'll give up to 32 participants repeat doses of the BEN8744 or placebo for 14 days. They'll take about 4 weeks to complete the study, stay on the ward for 17 nights and 18 days in a row and make 2 outpatient visits.

What are the possible benefits and risks of participating?
The researchers don't expect the study participants to get any medical benefit from the study medicine. The screening tests may be of benefit if an important medical problem is found, but they could reveal something people would prefer not to know about.

To date, no humans have taken BEN8744, so its side effects are unknown. The highest dose that researchers can give in this study is one that they predict will give blood levels of the medicine that were safe in animals. The researchers will monitor the participants closely, and increase the dose of BEN8744 only if the previous dose causes no important side effects. We'll withdraw participants if that's in their best interest. If a participant is withdrawn, they are asked to consent to a final follow up.

As BEN8744 enters the brain, volunteers are excluded from the study if they have ever attempted or contemplated suicide, assessed using the C-SSRS questionnaire at screening.

During their stay, participants must follow HMR's 'house rules'. An information leaflet is given to volunteers at screening. If a participant, or their partner, becomes pregnant during the study, they are asked to contact their GP about the pregnancy and this is documented using a generic information and consent form.

If the researchers find any medically important problem at screening, the physician will tell the participant in person, and pass on the results to the participant's GP. The researchers will contact participants' GPs to inform them that their patient has volunteered to take part in a study, and provide the GP with a study summary. For first-in-human studies, the researchers ask the GP if there's any medical problem that might compromise the volunteer's safety during the study. Participants consent to the researchers contacting their GP when they sign the ICF.

Please refer to the informed consent form for details on procedural risks, lifestyle and fasting restrictions, COVID-19 vaccine restrictions, and contraception requirements.

Where is the study run from?
HMR, London (UK)

When is the study starting and how long is it expected to run for?
May 2023 to March 2024

Who is funding the study?
BenevolentAI Cambridge Ltd (UK)

Who is the main contact?
Dr Kenneth Mulvany, legal@benevolent.ai

Contact information

Type(s)
Scientific

Contact name
Dr Kenneth Mulvany

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT06118385

Clinical Trials Information System (CTIS)
2022-003721-22

Integrated Research Application System (IRAS)
1006884

Protocol serial number
HMR code: 22-014, BB-8744-1001

Study information

Scientific Title
A randomised, double-blind, placebo-controlled, phase 1 first-in-human study to investigate the safety, tolerability, pharmacokinetics, and food effect of single- and multiple-ascending doses of BEN8744 in healthy subjects

Study objectives
Primary objectives:
1. To find out if BEN8744 has any important side effects in healthy men/women
2. To find out if food affects the absorption of BEN8744 into the bloodstream

Secondary objectives:
1. To find out how much BEN8744 is absorbed into the bloodstream and how long the body takes to get rid of it after single and repeat oral doses
2. To find out if BEN8744 has any important side effects in participants after high-fat food intake

Exploratory objectives (Part B and optional in Part C):
To find out levels of BEN8744 in urine and investigate BEN8744 and its metabolites (breakdown products) in plasma, urine, and faeces.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 04/07/2023, North – East York Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, HRA Newcastle, NE2 4NQ, UK), ref: 23/NE/0080
2. Approved 04/07/2023, MHRA (10 South Colonnade, Canary Wharf, London, E14 4PU, UK; +44 (0)20 3080 6000; info@mhra.gov.uk), ref: CTA 40491/0008/001-0001

Primary study design
Interventional

Study design
First-in-human safety, tolerability, pharmacokinetics and food effect trial in up to 108 healthy volunteers

Study type(s)
Safety

Health condition(s) or problem(s) studied
Healthy volunteers. Ulcerative colitis (UC).

Interventions
The study is in 3 parts: Part A (single doses), Part B (food effect) and Part C (repeated doses).

In Part A, up to 64 participants will be enrolled, in 6 groups of 8 (called Groups A1–A6) and 2 optional groups each of 8 participants (called Groups A7 and A8). Participants will have a single study session in which they will receive a single dose of BEN8744 or placebo by mouth. The dose participants receive will depend on their group; we plan to increase the dose as the study progresses. We plan to give the following doses:
1. Group A1: 2 mg
2. Group A2: 6 mg
3. Group A3: 20 mg
4. Group A4: 40 mg
5. Group A5: 80 mg
6. Group A6: 140 mg
7. Optional group A7: dose to be confirmed
8. Optional group A8: dose to be confirmed

Subsequent higher doses will only be tested if the previous dose causes no important side effects. At each dose level participants will be randomised to BEN8744 or placebo in a ratio of 3:1.

In Part B, up to 12 participants will be enrolled, in up to 2 groups of 6 (called Groups B1 and B2). Participants will have 2 study sessions. They will receive a single dose of BEN8744 by mouth in each session. They'll take the dose on an empty stomach in one of the sessions, and after a fatty breakfast in the other session. Doses will be decided after review of the results from earlier groups, including Part A of the study.

In Part C, up to 32 participants will be enrolled, in up to 3 groups of 8 (called Groups C1–C3) and 1 optional group of 8 participants (called Group C4). Participants will have a single study session. They will receive repeated doses of BEN8744 or placebo by mouth for 14 days. The dose participants receive will depend on their group. Doses will be decided after review of the results from earlier groups, including Part A of the study. At each dose level participants will be randomised to BEN8744 or placebo in a ratio of 3:1.

Participants will be dosed in the clinical unit and will remain on the ward until 3 days after their last dose in Parts A and C, and until 3 days after their dose in each session in Part B. They will have a final follow-up about 7 days after their last dose.

A computer program will decide randomly whether a participant takes BEN8744 or placebo.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
BEN8744

Primary outcome(s)
1. Safety and tolerability (Parts A and C): safety and tolerability of BEN8744, will be measured by standard Phase I unit monitoring.
1.1. Vital signs (blood pressure, pulse rate, tympanic temperature, and respiratory rate), 12-lead electrocardiogram (ECG), cardiac telemetry (Part A only), physical examination, laboratory safety tests (haematology, clinical chemistry, and urinalysis), and adverse events will be measured at screening, before dosing, at regular intervals up to 72 h after dosing and at the final follow-up visit
1.2. Observer's Assessment of Alertness/Sedation scale (OAAS/S), visual analogue scale (VAS) to monitor sedation will be measured before dosing, and at regular intervals after dosing
1.33. Columbia-Suicide Severity Rating Scale (C-SSRS) will be measured at screening, at 72 h after last dose and at the final follow-up visit (Part C only)
2. Pharmacokinetic parameters (Part B): plasma pharmacokinetic parameters of BEN8744 will be measured by solid phase extraction and liquid chromatography with tandem mass spectrometry before dosing, and at regular intervals up to 72 h after dosing in each treatment session.

Key secondary outcome(s)
1. Pharmacokinetic parameters (Parts A and C): Plasma pharmacokinetic parameters of BEN8744 will be measured by solid phase extraction and liquid chromatography with tandem mass spectrometry before dosing and frequently up to 72 h after dosing.
2. Safety and tolerability (Part B): Safety and tolerability of BEN8744 will be measured by standard Phase I unit monitoring
2.1. Vital signs (blood pressure, pulse rate, tympanic temperature, and respiratory rate), 12-lead ECG, physical examination, laboratory safety tests (haematology, clinical chemistry, and urinalysis), and adverse events will be measured at screening, before dosing, at regular intervals up to 72 h after dosing in each treatment session and at the final follow-up visit
2.2. OAAS/S and VAS to monitor sedation will be measured before dosing, and at regular intervals up to 72 h after dosing in each treatment session

Completion date
18/03/2024

Eligibility

Key inclusion criteria
1. Aged 18–65 years
2. Body mass index 18.0–30.9 kg/m2
3. In good health, as judged by medical history, medical examination, vital signs, ECG and clinical laboratory tests
4. Able to communicate with study personnel

5. Reliable, willing, and likely to comply with the protocol
6. Willing to comply with the contraception of the protocol
7. Consent to our informing their GP of their participation in the study, and to our entering their details into the over-volunteering database (TOPS)

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
65 Years

Sex
All

Total final enrolment
76

Key exclusion criteria
1. Not healthy (clinically significant abnormality in our screening tests, which include ECG, vital signs, physical examination, and laboratory safety tests of blood and urine);
2. Abuse of alcohol or drugs
3. Taken prescription medicine or a COVID-19 vaccine during the 28 days before dosing; taken other medicine (except up to 2 g paracetamol), herbal remedies or dietary supplements during the 7 days before dosing; have had a serious reaction to any medicine
4. Have had any condition or operation that might affect the way the body absorbs medicines or have had any clinically significant disease
5. History of seizures or at risk of seizure (eg history of significant head trauma)
6. Significant suicidality history or suicidality risk (assessed by C-SSRS)
7. Objection by GP on medical grounds — because they might increase the risk, or confound the assessment of BEN8744. Mental illness might compromise consent.
8. Pregnant or breastfeeding or unwilling to comply with the contraception requirements of the protocol — because of the potential risk to the unborn or breastfed baby
9. Have donated blood, or taken part in another study, within the past 3 months or don't agree not to donate blood, or take part in another study, during the 3 months after this study
10. Regular users of cigarettes or tobacco and/or nicotine-containing products (including e-cigarettes) in the 3 months before screening. Social smokers or vapers who smoke/vape in the 1 month before screening.
11. Unwilling to eat a high-fat breakfast containing bacon — because, to study the effects of food on blood levels of the study medicine, we must give all participants the standard high-fat breakfast specified by the US Food and Drug Administration (Part B only)

Date of first enrolment

13/07/2023

Date of final enrolment
18/03/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
HMR
Cumberland Avenue
Park Royal
London
England
NW10 7EW

Sponsor information

Organisation
BenevolentAI Cambridge Ltd

Funder(s)

Funder type
Industry

Funder Name
BenevolentAI Cambridge Ltd

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results			09/04/2026	No	No