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A phase I (food effect and multiple ascending dose) trial with DNDI-6899

Submission date
04/05/2024

Recruitment status
No longer recruiting

Registration date
23/09/2024

Overall study status
Ongoing

Last Edited
10/09/2026

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
DNDI-6899 is a new medicine being developed for the treatment of a disease called Visceral Leishmaniasis (VL), which is a disease caused by a parasite (an organism that lives in a host and gets its food at the expense of its host). It is common in areas such as East Africa, India and Brazil. The trial will be done in 2 parts: Part A and B, with up to 36 participants in total.

Who can participate?
Healthy volunteers aged 18 - 55 years.

What does the study involve?
Part A is to look at two single doses to test the effect of food on the absorption of the trial medicine into the body. Participants will undergo treatment in both fed and fasted states.
Part B is blinded and is to look at increasing the dose from one small group of participants to the next, to find a safe dose.

Part A:
Part A will consist of testing two single doses of IMP in two treatment periods: fed and fasted. After consent and eligibility checks, participants will be admitted to the NIHR Clinical Research Facility (CRF) at the Liverpool University Hospitals NHS Trust twice for 6 days. Participants will take 500mg of DNDi-6899 under two treatment phases: both fed and fasted, of 6 days each. The first treatment phase will be determined by random allocation, followed by a 10-day washout period. Treatment will then commence under the opposite treatment allocation. Follow-up will take place approximately 14-21 days after, with frequent blood tests and procedures to test safety. WOCBP will return for a final follow-up visit at 28 days (WOCBP only).

Part B:
Part B will consist of up to 3 groups of participants with 8 in each group. Part B will be blinded (DNDi-6899 or placebo) so participants will not know which treatment they will receive. Part B will be to look at the dose escalation of DNDi-6899, with safety meetings after each cohort to review safety data and give permission to dose escalate if the product is proven to be safe.

Participants will be admitted to the CRF for 15 days with follow-ups 14-21 and 28 days (WOCBP only) after discharge from the CRF.
All participants will be reimbursed.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
1. Safety of IMP
The main risk to participants is the safety of IMP. The IMP has been tested in animals so there is some toxicity data. Participants will be closely monitored and treated on an MHRA-accredited CRF. A robust eligibility assessment will be carried out. ECGs, blood and urine tests and eye tests will be carried out regularly, and participants will be followed up 14-21 days after discharge from the facility. Further testing will be at the discretion of the PI if required. For women of childbearing potential, a pregnancy test will be carried out again at 28 days. A Dose Escalation Committee will be set up. The dose will not be escalated unless there is clear evidence that the IMP is safe. There is a risk of potential drug:drug interactions. Safety procedures will be in place, with a safety management plan and safety group to review safety as the trial takes place. Participants will be required to consent to using adequate contraception during and for a certain amount of time after discharge from the CRF. As Part B is blinded, an Independent Data Monitoring Committee will be set up to look at unblinded data if required.
2. Sponsor is located outside the UK
The sponsor is DNDi based in Switzerland. A set-up agreement has been signed and set-up meetings have taken place. A further agreement (for trial conduct) will be signed before the start of recruitment. The sponsor has established a working relationship with staff from the University of Liverpool (UoL) and the Liverpool University Hospital. UoL has agreed to act as UK Legal Representative of the sponsor and this will be written into the conduct agreement between DNDi and UoL. The sponsor has performed qualification audits for the CRF and UoL. The trial is single site only.
3. IMP transfer, manufacturing and QP release
IMP manufacture is being managed by the sponsor, located outside the UK. UoL and DNDi will work with Copea, a reputable organisation based in Liverpool for transfer, manufacturing and QP release. IMP will be stored by Copea and ordered by site as required. Copea staff will review the Investigational dossier, provide labelling and oversee QP release.
4. Consent procedures and participant understanding
Consent will take place according to written procedures at the CRF by appropriately qualified staff. Only participants aged 18-55 will be approached for consent. A robust exclusion criteria is in place.
5. Inconvenience of being an in-patient and multiple interventions
Participants will be required to be treated in fed and fasted conditions in part A, this will mean duplicated in-patient stay and interventions. Appropriate advertising will take place through a recruitment plan which has been submitted for REC review. Participants will receive a stipend for the inconvenience of being an inpatient and the interventions. Recruitment will be monitored by the Trial Management Group (TMG) and action will be taken to increase exposure to adverts if required, and to expand recruitment strategies. Safety will also be monitored by the TMG.
6. Confidentiality
Only safety data will be transferred to DNDi as the sponsor. This will be specifically for the purposes of reporting Serious Adverse Events (SAEs). This data will be anonymised. DNDi will have access to data during Dose Escalation meetings and at the end of the trial, but this will be presented in an anonymised format. Personal data will be transferred out of the NHS Trust to the University of Liverpool. Anonymised data will be transferred to labs outside the UK for

various analyses. The PIS gives details of steps taken to maintain confidentiality. Participants will provide consent for appropriate individuals to access personal data, e.g. for assessment, treatment, monitoring, reimbursement and inspection purposes. On enrollment, participants will be allocated a trial identification number which will be used throughout the trial. Only anonymised data will be used for analysis and publication and individual participants will not be identified. When participants are discussed during meetings, their confidentiality will be maintained and they will be referred to by trial identification number only.

Where is the study run from?
University of Liverpool (UK)

When is the study starting and how long is it expected to run for?
July 2023 to December 2027

Who is funding the study?
Drugs for Neglected Diseases Initiative (Switzerland)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

Integrated Research Application System (IRAS)
1009683

Protocol serial number
DNDi-6899-01

Study information

Scientific Title
A phase I double-blind, placebo-controlled (part B only), randomised trial to evaluate the safety, tolerability and pharmacokinetics of single dose in fed state, and repeated doses of DNDI-6899 in healthy participants

Acronym
DNDi-6899

Study objectives
Primary objective:
1. To evaluate the safety and tolerability of single and repeat doses of DNDI-6899 in healthy participants

Secondary objectives:
1. To evaluate the systemic PK profile of single dose of DNDI-6899 under fasted and fed conditions and repeat doses of DNDI-6899 in healthy participants
2. To examine the food effect of DNDI-6899
3. To examine dose proportionality following multiple doses of DNDI-6899
4. To assess accumulation and time invariance ratios of DNDI-6899 after multiple doses

Exploratory Objectives:
1. To assess urinary metabolites
2. To assess the effect of DNDI-6899 on Holter electrocardiograms parameters
3. To investigate any potential changes to exploratory renal biomarkers
4. To assess variation of mRNA expression in full blood before and after exposure to the drug (transcriptional profiling in Part B (MAD) only)

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 28/06/2024, Greater Manchester Central Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8004; gmcentral.rec@hra.nhs.uk), ref: 24/NW/0121

Primary study design
Interventional

Study design
Interventional randomized, Part A: Unblinded, Part B: Blinded

Study type(s)
Safety

Health condition(s) or problem(s) studied
Healthy volunteers to test a treatment for Visceral Leishmaniasis

Interventions
This trial will be a double-blind placebo-controlled (Part B only), randomised trial to evaluate the safety, tolerability, and pharmacokinetics of single dose in fed state, and repeat doses of DNDI-6899 in healthy participants.
This trial is planned to ensure that a target of 36 evaluable participants will be randomised and will consist of two parts.
PART A (FOOD EFFECT):
Cohort 1 will comprise of 2 treatment periods and investigate the effect of food on the safety, tolerability and PK of a 500 mg single oral dose of DNDI-6899, previously selected from SAD GSK3186899 trial in fasted conditions. Cohort 1 will consist of up to 14 healthy participants to get 12 evaluable participants. Each participant will receive a maximum of 2 oral doses of DNDI-6899, one under fasted and one under fed conditions (with a 'wash out' period in between these doses). Blood and urine samples will be collected under both fed and fasted conditions for the analysis of DNDI-6899 and metabolites in plasma – pharmacokinetic (PK) evaluation.

PART B (MULTIPLE ASCENDING DOSE):
Part B will comprise of the repeat dose escalation phase. There will be up to 3 cohorts (Cohorts 2, 3 and 4), each cohort consisting of 8 healthy participants. Participants will only participate in one cohort. In each cohort, participants will be randomised in a 3:1 ratio to receive repeat doses of either DNDI-6899 or placebo, according to the randomisation schedule, in a blinded manner. DNDI-6899 or placebo will be administered twice-daily (BID) dosing orally with a 12-hour dosing interval for 9 days. On Day 10 participants will receive only a morning dose of DNDI-6899 or placebo.
Participants are planned to receive each dose in fasted conditions. However, depending upon the interim results from Part A, it may be decided to dose DNDI-6899 and placebo in fed conditions. This will be subject to decision by the Dose Escalation Review Committee (DERC) at the end of the Part A.

DOSAGE SCHEDULES:

Part A - Food Effect:
• Dose cohort 1: 500 mg (1 dose of treatment for fed regimen and 1 dose of treatment for fasted regimen). Treatment regimens will be randomised. There will be 12 evaluable participants in total.
Participants taking part in PART A cannot take part in PART B.

Part B - Multiple Ascending Dose:
Participants will be randomised to active IMP or placebo and can only take part in one cohort.
• Dose Cohort 2: 150mg, 10 days of treatment, twice daily dosing (BID) administered using a 12hr dosing interval (6 participants active, 2 placebo), except for D10 single morning administration.
• Dose Cohort 3: exact dose to be defined during DERC meeting after review of data from previous cohort, 10 days of treatment, twice daily dosing (BID) administered using a 12hr dosing interval (6 participants active, 2 placebo), except for D10 single morning administration.

• Dose Cohort 4: projected 500mg, 10 days of treatment, twice daily dosing (BID) administered using a 12hr dosing interval (6 participants active, 2 placebo), except for D10 single morning administration.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
DNDI-6899

Primary outcome(s)
To evaluate the safety and tolerability the participant will be monitored after taking IMP and at various timepoints after. Vital signs will also be taken regularly.
1. Adverse events
2. Clinically important laboratory values
3. PCI vital signs
4. 12 lead electrocardiogram (ECG) findings
5. 24 hours (hr) telemetry and Holter findings
6. Physical examination findings

Key secondary outcome(s)
1.Plasma concentrations of DNDI-6899 plus derived parameters, as data allow.
For Food Effect part: Derived PK parameters for DNDI-6899 following single dose under fasted and fed conditions including area under the plasma drug concentration versus time curve (AUC(0-t), AUC(0-∞), maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (Tmax), and apparent terminal half-life (T1/2) as data allow.
For Multiple Ascending Dose part: derived PK parameters^ : AUC(0-t), AUC (0-∞), AUC(0-tau), Cmax, Tmax, Ctau and T1/2.
Strategy:
For the fed/fasted part:
Fed PK parameters will be included if the participant had the fed dose and PK parameter from the fed part, and similarly for the fasted PK parameters.
Multiple ascending dose part:
Day 1 parameters will be included if the participant had Day 1 dose and Day 1 PK parameter available. Day 10 parameters will be included only if participant had all 10 doses and had Day 10 PK parameter available.
Summary measure:
For each group, geometric means of AUC(0-t), AUC (0-∞), AUC(0-tau), Ctau and Cmax, median of Tmax and arithmetic mean of T1/2.

2. Food effect assessment using derived PK parameters^: AUC(0-t), AUC(0-∞), T1/2, Tmax and Cmax.
Strategy:
Participants must have both fed and fasted doses. In addition, participants who do not have a particular PK parameter from both the fed and fasted doses will be excluded for that PK parameter.
Summary measure:
Geometric mean ratios fed:fasted for AUC(0-t), AUC(0-∞), T1/2, Tmax and Cmax.

3. Dose-proportionality assessment using derived PK parameters^: AUC(0-tau), Tmax, Cmax, Ctau.
Strategy:
Data will be reported based on complete dosing and PK parameters from Day 10. That is, data from participants who do not complete all 19 doses will be excluded from analyses, and participants who do not have a particular PK parameter on Day 10 will be excluded for that PK parameter.
Summary measure:
Slope from power model for AUC(0-tau), Ctau and Cmax across the 3 doses at Day 10.

4. Accumulation and time invariance ratios of DNDI-6899 after multiple doses.
PK parameters from Day 1 and Day 10: AUC(0-tau), Cmax, Ctau; PK parameters^ AUC (0- 12) on Day 10 and AUC (0-∞) on Day 1.
Strategy:
Data will be used from participants taking all 19 doses and having PK parameters from Day 1 and Day 10. That is, data from participants who do not complete all 19 doses will be excluded from analyses, and participants who do not have the appropriate PK parameter from both Day 1 and Day 10 will be excluded for that PK parameter.
Summary measure:
Accumulation ratios * RAUC(0-tau), RCmax and RCtau. Time-invariance ratio calculation as AUC (0- 12) on day 10 to AUC(0-∞) on day 1.

Exploratory Endpoints
1. Urine samples will be collected for analysis of metabolites of DNDI-6899.
2. 24 hour/48 hours Holter ECG will be recorded at regular intervals during the trial and analysed centrally to assess the effect of DNDI-6899 on Holter electrocardiogram parameters.

Completion date
31/12/2027

Eligibility

Key inclusion criteria
1. Participants must be 18 to 55 years of age inclusive, at the time of signing the informed consent and can be included in only one cohort of this trial.
2. Participants must be healthy as determined by the Investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.
3. Body weight ≥50 kg and body mass index (BMI) within the range 18.5 -30 kg/m² (inclusive).
4. Male Participants:
Male participants with partners of childbearing potential must use either one of the male or female condom, with the female partner using an additional highly effective contraceptive method with a failure rate of <1% per year, during the treatment period, and for at least 90 days after the last dose of trial treatment.
Other acceptable methods of contraception include:
• Any highly effective method of contraception listed below for female participants
• Progesterone-only oral contraception, where inhibition of ovulation is not the primary mode of action
• Cap, diaphragm, or sponge with spermicide
For participants who practice true abstinence, when this is in line with the preferred and usual lifestyle of the participant, contraceptive requirements do not apply.

Male participants should refrain from donating sperm during the treatment period and for at least 90 days after the last dose of trial treatment.
For participants who are exclusively in same-sex relationships, contraceptive requirements do not apply.
5. Female Participants:
Female participants who are of non-childbearing potential (i.e., due to being post menopausal for at least 1 year (confirmed by FSH assessment) or permanently sterile following hysterectomy, bilateral salpingectomy, bilateral oophorectomy) will not be required to use contraception.
Female participants of childbearing potential must be willing to use a highly effective method of birth control (i.e. contraceptive measure with a failure rate of <1% per year when used consistently and correctly, as per described in protocol) with low user dependency, in conjunction with a barrier contraception (i.e. either one of the male or female barrier contraceptions) from the time of screening until 30 days after the final Follow up Visit. Use of any of the protocol defined contraception should have been established for at least 90 days prior to enrolment (the investigator should evaluate the potential for contraceptive method failure (e.g. non-compliance, recently initiated) in relationship to the first dose of trial treatment.
Highly effective methods of contraception include:
• Placement of intrauterine device or intrauterine system.
• Established use of oral, injected or implanted hormonal methods of contraception associated with inhibition of ovulation.
• Male sterilisation (with the appropriate post-vasectomy confirmation of surgical success). For female participants on the trial, the vasectomised male partner should be the sole partner for that participant.
• Bilateral tubal ligation
For participants who practice true abstinence, when this is in line with the preferred and usual lifestyle of the participant, contraceptive requirements do not apply.
For participants who are exclusively in same-sex relationships, contraceptive requirements do not apply.
6. Willing to participate in the trial and capable of giving signed informed consent.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
All

Total final enrolment
36

Key exclusion criteria

1. History or presence of current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the trial treatment; or interfering with the interpretation of data in the opinion of the investigator.
2. Previous history of leishmaniasis
3. Alanine transaminase (ALT) or Aspartate aminotransferase (AST) >upper limit of normal (ULN) confirmed by repeat assessment.
4. Bilirubin >ULN confirmed by repeat assessment. Participants with known Gilbert's syndrome with total bilirubin < 1.5xULN are eligible to participate in the study.
5. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of asymptomatic gallstones)
6. Current or past history of clinically significant gastritis or gastroduodenal ulcers
7. Regular use of non-steroidal anti-inflammatory drugs (NSAID)
8. QTcf >450 msec for male and 470 msec for female
9. Loss of blood or blood products in excess of 500 mL within a 56-day period.
10. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current trial: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
11. Sensitivity to any of the trial treatments, or components or drug or other allergy that, in the opinion of the Investigator or DNDi Medical Monitor, contraindicates participation in the trial.
12. Regular use of known drugs of abuse.
13. Participants with an estimated GRF (calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation) of ≤ 80ml/min/1.73m2 or with significant hematuria or proteinuria (+or higher)on urinary dipstick testing.
14. Presence of Hepatitis B surface antigen (HBsAg) or positive Hepatitis C antibody test result at screening.
15. Positive human immunodeficiency virus (HIV) antibody test.
16. Positive pre-trial drug/alcohol screen (confirmed by repeat exam).
17. Clinically significant proteinuria and or haematuria, defined as positive urine dipstick test (1+). Urine dipstick should be repeated at least 3 days apart in case of urine dipstick test trace reading on previous occasion.
18. Participants with Spot urine protein creatinine ratio >0.5 will be excluded.
19. History or regular use of tobacco or nicotine-containing products within 3 months prior to screening.
20. Systolic BP of less than or equal to 90.
21. Use of vitamins, herbal therapies, minerals, supplements during 14 days before the first dose of trial medication (except St John's Wort). Prescription medicine during the 14 days before the first dose of trial medication or use of an overthecounter medicine during the 14 days before the first dose of trial medication (with the exception of the oral contraceptive pill or up to 2g of paracetamol daily).
22. Participants must not have travelled to an area (as determined by the investigator) with a high prevalence of leishmanial/parasitic infections in the 6 months before screening or intend to do so in the 3 months after the final dose of trial treatment.
23. Food Effect part only: Participant must have no dietary restrictions (e.g., lactose intolerance) or inability to eat an adapted standard meal (includes 35-40% fat content).
24. Food Effect part only: History of gall bladder surgery or gall bladder removal, or history of an acute disease state (e.g., cholelithiasis) within 14 days prior to receiving the trial treatment.
25. Any other condition or consideration that, in the opinion of the investigator or DNDi Medical Responsible, would pose a health risk to the participant if they were enrolled in the study or

would otherwise interfere with the evaluation of the study aims.
26. Pregnant or breastfeeding women.
27. Hypersensitivity to the IMP active substance or to any of the excipients.
28. History of clinically significant ocular conditions or abnormal findings during ocular examination at screening.

Date of first enrolment
30/09/2024

Date of final enrolment
22/04/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Liverpool Clinical Research Facility (NIHR CRF)
Royal Liverpool University Hospital
Liverpool University Hospitals NHS Foundation Trust
Prescott Street
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Sponsor information

Organisation
Drugs for Neglected Diseases Initiative

ROR
https://ror.org/022mz6y25

Funder(s)

Funder type
Research organisation

Funder Name

Drugs for Neglected Diseases initiative

Alternative Name(s)
DNDi

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
The University of Liverpool has a policy for data sharing. This is written by the infection pharmacology group and has been approved by the University sponsor representatives. The policy includes, a requirement to complete a data sharing form, giving an outline of the reasons for the request. For this trial, it is likely that requests for data sharing from other organisations will be directed to DNDi as sponsor. Participants will consent for their samples to be included for future use in research at other institutions, when they sign the Informed Consent Form.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Other files	SPIRIT checklist		17/06/2026	No	No