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 repeat doses of DNDI-6899 in healthy participants

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Background

Visceral Leishmaniasis (VL) – also known as Kala-azar – is a disease caused by obligate intracellular protozoan parasites, particularly the species *Leishmania donovani* and *Leishmania infantum*. VL causes fever, weight loss, severe haematological damage, spleen and liver enlargement, and, if left untreated, cases of VL are typically fatal. Despite the significant change in the epidemiology of the disease in recent years, VL remains a major problem in Africa but also in the Americas. The main barrier to the elimination goal refers to the difficulty in offering accessible, effective and safe treatments. While therapies are available to treat the disease, none are ideal for use in resource poor settings where the disease is endemic, due to the unfavourable safety profile of drugs, logistical complexity and cost. As such there is a real unmet medical need for new, short course oral drugs for the treatment of this disease. DNDI-6899 is a novel pyrazolopyrimidine derivative that has the potential to be effective against VL.

Methods

This is a first in human clinical investigation with Food Effect (Part A) and Double-Blind Multiple Ascending Dose (Part B) in healthy participants. In Part A, 12 participants will be randomised to fed or fasted conditions (treatment period 1) and dosed with DNDI-6899. The same participants will then be treated under opposite conditions (treatment period 2) after an appropriate washout period. In Part B, participants will be randomised to either DNDI-6899 or placebo in either fed or fasted conditions. Treatment conditions in Part B will depend on the results in Part A.

Conclusions

This trial will assess the safety, tolerability, and pharmacokinetics of single and repeat doses of DNDI-6899 in healthy participants.

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Keywords

Visceral Leishmaniasis, phase I, food effect, dose escalation, treatment period

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Abbreviations

AE	Adverse Event
BID	"Bis In Die" – Twice a day
BP	Blood Pressure
DERC	Dose Escalation Review Committee
ECG	Electrocardiogram
FE	Food Effect
GP	General Practitioner
HR	Heart Rate
HCG	Human Chorionic Gonadotropin
IB	Investigator Brochure
IDSMB	Independent Data Safety Monitoring Board
IMP	Investigational Medicinal Product
LCTC	Liverpool Clinical Trial Centre
MAD	Multiple Ascending Dose
MR	Medical Responsible
NIHR CRN	National Institute for Health Research Clinical Research Network
NOAEL	No Observed Adverse Effect Level
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PIC	Participant Identification Centre
PK	Pharmacokinetics
QC	Quality Control
GPQ	General Practitioner Questionnaire
RSI	Reference Safety Information
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SoA	Schedule of Assessments
SUSAR	Suspected Unexpected Serious Adverse Reaction
WOCBP	Women of Childbearing Potential
WONCBP	Women of Non-Childbearing Potential

Plain Language Summary

Visceral Leishmaniasis is a parasite transmitted to humans through bites from infected sandflies. The parasite increases in number in the body to affect internal organs such as the spleen and liver. This can lead to death if left untreated.

Available treatments are not ideal for use due to cost, the need for cold chain, and side effects. New drugs that can be taken by mouth are urgently needed.

DNDi-6899, a novel treatment works by blocking two proteins present in the parasite, leading to its death. This trial will answer the following:

- Does the trial drug have any important side effects?
- Does food affect absorption of the drug into the bloodstream?
- How does the body handle the drug?
- How long does the body take to get rid of it?

In certain groups, there will be assessments of variations in certain biomolecules in the body before and after exposure to the new treatment DNDI-6899.

Introduction

Visceral Leishmaniasis (VL) is spread by the bites of phlebotomine sandflies. VL causes fever, weight loss, severe haematological damage, spleen and liver enlargement, and, if not treated, death. In all endemic regions, current standards of care have significant limitations, including toxicity, operational complexity such as cold-chain requirements and administration costs, and inconvenience caused to patients, such as pain and the need for prolonged hospitalisation. Receiving treatment often requires individuals, who are already very unwell, to travel sometimes from remote, hard to reach areas to a medical facility for repeat treatments.

DNDI-6899, formerly known as GSK3186899, is a novel pyrazolopyrimidine derivative that is an inhibitor of Leishmania Cdc2-related kinase 12 (CRK12), with an antiparasitic effect, indicated for the treatment of Visceral Leishmaniasis.[5] The company GSK carried out a single ascending dose study in healthy volunteers up to 800 mg in a fasted state with a preliminary formulation deemed suitable for phase 1. DNDi has subsequently taken over clinical development with this phase I trial (using the same formulation) which is described below. In parallel, DNDi is developing a new formulation suited for administration to people living with VL in endemic regions.

Protocol

The DNDi-6899-01 study will be a first in human clinical investigation with Food Effect (Part A) and Double-Blind Multiple Ascending Dose (Part B) in healthy participants. The study will be performed at a single centre, the NIHR Liverpool Clinical Research Facility (CRF) which is an MHRA-accredited Phase I unit in the UK. Study design incorporates a randomised sequence (fed-fasted) for part A, and placebo-controlled double blind (for part B) with initial safety evaluations and pharmacokinetic measurements undertaken blinded to allocation. Interim data will be reviewed by a Dose Escalation Review Committee (DERC) and ratified by an independent IDSMB as required.

Dose selection for this trial was based on in silico modelling using the results from the SAD trial and non-clinical studies. Based on these results, the dose 500 mg BID has been selected as the top dose for the MAD part of the trial. Three dose levels will be explored. The starting dose will be 150 mg BID, expected to provide approximately 20% of the exposure of the top dose. The intermediate dose is currently projected to be 300 mg BID, providing approximately

50% of the top dose exposure, however this will be reassessed during the trial conduct based on emerging data. Food effect will be studied as a single dose of 500 mg, the maximum dose to be used in the multiple ascending dose study (Part B). The initial protocol version 2 was approved by the Central Manchester Research Ethics Committee, UK on 27th June 2024, and by the UK regulator the Medicines and Healthcare products Regulatory Agency (MHRA) on the 5th July 2024.

Part A (Food Effect):

Cohort 1 will investigate the effect of food on the safety, tolerability and PK of a 500 mg single oral dose of DNDI-6899 in up to 14 healthy participants to obtain 12 evaluable participants. Each participant will be randomised to receive a single 500mg oral dose of DNDI-6899, under fasted or fed conditions (Treatment Period 1) then after a washout of at least 10 days be dosed within opposite condition for Treatment Period 2. Participants in Part A will not be allowed to participate in Part B. All participants will be admitted for an overnight fast, and participants assigned to fed conditions will receive a breakfast comprising the standard FDA breakfast.

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 for 10 days with a 12-hour dosing interval (+/- 10 minutes). As Part B will be the first time DNDI-6899 is administered to humans as twice-daily dosing on successive days **(except on Day 10, only morning dose)**, the trial design and especially the dose of the intermediate cohort (Cohort 3), will be decided by the DERC during trial conduct based on emerging data as the trial progresses. Each new dosing tier will be commenced with a sentinel review of the first two participants prior to recruiting the rest of the cohort. Details regarding the sentinel arrangements are in the breakdown of Part B below.

Trial objectives

The primary objective is to evaluate the safety and tolerability of single (part A) and repeat (part B) doses of DNDI-6899 in healthy participants. Secondary objectives are 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, to evaluate the impact of food, to characterise dose proportionality following multiple doses of DNDI-6899 and to assess accumulation and time invariance ratios of DNDI-6899 after multiple doses. Exploratory objectives are to assess urinary metabolites and the effect of DNDI-6899 on Holter electrocardiogram parameters.

Study population

A sufficient number of participants will be screened to ensure that a target of 36 evaluable participants will be randomised (target Part A: 12 evaluable participants; Part B: 8 evaluable participants into each of the 3 Cohorts for a total of 24 participants). Participants are considered evaluable if they complete both screening and at least one treatment period in Part A, or the 10-day treatment period in Part B. Participants that take part in Part A of the trial cannot participate in Part B.

Inclusion criteria

1. Healthy participants aged 18 to 55 years.2. Body weight ≥50 kg and body mass index (BMI) 18.5 - 30 kg/m2.

2. Male participants with partners of childbearing potential must use barrier contraception, with female partners using an additional highly effective contraceptive method. Female participants of childbearing potential must be willing to use a highly effective method of birth control from the time of screening until 30 days after the final visit. Female participants who are of non-childbearing potential, and participants who are exclusively in same-sex relationships will not be required to use contraception.

Exclusion criteria include:

1. Participants with cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs. Participants with evidence of hepatitis B or C or HIV, or a systolic BP of less than 90mmHg, or QTcF >450 msec (males) and 470 msec (female).

2. Previous history of leishmaniasis or travel to an area with a high prevalence of leishmanial/parasitic infections (within 6 months).
3. Known hepatic or biliary disease, or alanine/aspartate transaminase above upper limit of normal (ULN). Bilirubin >ULN unless known to have Gilbert's syndrome (if total bilirubin is <1.5ULN). Current or past history of clinically significant gastritis or gastroduodenal ulcers, and loss of blood or blood products in excess of 500 mL.
4. eGFR of ≤ 80ml/min/1.73m^2 or significant hematuria or proteinuria.
5. History of clinically significant ocular conditions or abnormal findings during ocular examination at screening.
6. Regular use of non-steroidal anti-inflammatory drugs (NSAID), drugs of abuse, tobacco or nicotine-containing products (within 3 months), vitamins, herbals (within 14 days), St John's Wort (within 28 days), positive drug/alcohol screen. Sensitivity to any of the trial treatments, or components or drug or other serious allergy.
7. Women who are pregnant or breastfeeding.

Food Effect part only: dietary restrictions or inability to eat an adapted standard meal. History of gall bladder disease (within 14 days).

Blinding and Dosing

Part A - Food Effect will be open label:

Dose cohort 1: 500 mg single dose, in fed and fasted state (sequence will be randomised) (N=12). Part B - Multiple Ascending Dose will comprise 3 cohorts randomised to treatment (N=6) or placebo (N=2), with double blinding of allocation: i) Cohort 2 will evaluate DNDi-6899 at 150mg bid for 10 days, ii) Cohort 3 will evaluate DNDi-6899 at a dose between 150-500mg (determined by DERC), iii) Cohort 4 will evaluate DNDi-6899 at a dose no higher than 500mg bid for 10 days.

Trial procedures

Physical examination, vital signs and ECG will be recorded as shown in tables 1 and 2. In addition, 48-hour Holter ECG monitoring will assess the effect of DNDI-6899 for both parts A and B. Non-invasive visual acuity assessments using the Early Treatment Diabetic Retinopathy Study chart will be undertaken. Characterisation of plasma pharmacokinetics include rich sampling (pre-dose and post dose, 10 minutes, 30 minutes, 1 hour, 1.5 hours, 2

hours, 2,5 hours and then 3-6 hours) for Part A, and for Days 1 (first dose) and 10 in Part B, with additional pharmacokinetic samples taken at Day 1 (second dose; 0, 1 and 3 h) and daily (random sampling) until Day 9.

TABLE 1: SCHEDULE OF ASSESSMENTS – PART A FOOD EFFECT									
Procedure	**Screening -28 days**	**Trial period (Days). Repeated for Treatment Period 2.**						**Follow-up (14-21 days)**	**Follow-up (28-31 days) WOCBP only**
		D-2	D-1	D1	D2	D3	D4		
Outpatient Visit	x							x	x
Informed consent	x								
Admission		x							
Inpatient Stay		<---------->							
Inclusion and exclusion criteria	x		x						
Demography	x								
Full physical examination	x		x						
Brief physical examination					x		X	x	
Drug/Alcohol/Smoking Screen	x		x						
Medical/Medication/Drug/Alcohol history	x								
HIV and Hepatitis B and C Screening	x								
Follicle stimulating hormone (FSH) + Oestradiol	x								
Standard HCG pregnancy test	x		x				X		x
Holter Monitoring (48 hours)			<---------->						
Haematology/ Clinical Chemistry	x		x		x		X	x	
Urine Sampling				x					
Exploratory renal biomarkers				x			X		
12-Lead ECG	x		T	T*	T	<-T->		T	
Vital Signs	x		x	T	x	<-x->		x	
Telemetry				<-x->					
Visual Acuity	x		x	x			X	x	
PK Blood Sampling				x	x				
Meals		x	x	x	x	x	X		
Randomisation			x						
IMP administration				x					
AE review	x	<<----------x-------->>						x	x
SAE review	x	<<----------x-------->>						x	x
Concomitant medication review	x	<<----------x-------->>						x	x
Discharge							X		

TABLE 2: SCHEDULE OF ASSESSMENTS – Part B MULTIPLE ASCENDING DOSE																		
Procedure	**Screen -28 days**	**Trial Period (Days)** T = Triplicate															**Follow-up (14-21 days)**	**Follow-up (28-31 days) WOCBP only**
		-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13		
Outpatient Visit	x																x	x
Informed consent	x																	
Admission		x																
Inpatient Stay		<<----------x----------->>																
Discharge																x		
Inclusion and exclusion criteria	x		x															
Demography	x																	
Full physical examination	x		x															
Brief physical examination					x					x						x	x	
Drug/alcohol/smoking screen	x	x																
Medical/drug history	x																	
HIV, Hepatitis B and C	x																	
FSH + Oestradiol	x																	
Standard HCG pregnancy test	x		x													x		x
Holter Monitoring			<----->										<----->					
Haematology/ Clinical Chemistry	x		x		x		x		x		x		x		x	x	x	
Exploratory renal biomarkers				x	x		x						x					
Transcriptomics blood sampling			x										x					
Randomisation				x														
IMP administration				x	x	x	x	x	x	x	x	x	x					
Visual Acuity	x		x	x			x						x			x	x	
Telemetry				x	x													
12-Lead ECG	x		T	T	T		T		T		T		T		T	T	T	
Vital Signs	x		x	T	x	x	x	x	x	x	x	x	x	x	x	x	x	
Urine Sampling				x									x					
Meals		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
PK sampling				<<----------x----------->>														
AE review	x	<<----------x----------->>															x	x
SAE review	x	<<----------x----------->>															x	x
Concomitant medication review	x	<<----------x----------->>															x	X

Participant withdrawals and stopping criteria

Individual participants will have treatment discontinued if they experience a serious or severe AE related to investigational product, become pregnant, initiate treatment with any prohibited medications, develop significant liver, renal or cardiac (QTcF) toxicity or develop gastric erosions.

Dosing cohorts will be stopped if any of these criteria is met:

i) two or more participants in the same cohort experience a severe non-serious adverse reaction

ii) two or more participants across all trial parts develop an adverse renal event (clinically significant and persistent haematuria / proteinuria, or change in serum creatinine > 26 µmol/L or >50% from baseline, or persistent hypophosphataemia, or >25% increase in serum Cystatin C.

iii) two or more participants in the cohort experience individual liver related AE, QTcF prolongation or stomach erosions as defined in individual stopping criteria.

iv) one or more participants from any dose level experiences a serious adverse event which has a reasonable possibility of relation to trial drug.

Additional pharmacokinetic stopping criteria will be applied. A maximum Cmax of 15.4µg/mL and, AUC(0-12h) of 72.3 µg.h/mL for MAD part will not be exceeded in an individual subject and will be used as safety threshold exposures for PK stopping criteria, based on a three-fold safety margin from the corresponding values at the NOAEL in female rats (Cmax of 46.2 µg/mL and AUC (0-12h) of 217 µg.h/mL).

Trial governance

The Trial Management Group will oversee day-to-day running of the trial. The Dose Escalation Review Committee reviews blinded safety, PK and other relevant data before allowing progression from Part A to Part B, and then after each cohort in Part B before progression and dosing of the next cohort.

An Independent Data and Safety Monitoring Board will be established for Part B for the purposes of an unblinded review of safety data should it be required.

Assessment of safety

AE: any untoward medical occurrence in a trial participant, to whom a medicinal product is administered, and which does not necessarily have a causal relationship with this treatment.

SAE: any untoward medical occurrence that, at any dose, meets the definition of serious.

(S)AR: An adverse event, whether serious (SAR) or non-serious (AR), that is in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

SUSAR: A serious adverse reaction, the nature and severity of which is not consistent with the information given in the safety information for the medicinal product.

Table 3: Severity definition

Mild:	The participant is aware of the event or symptom, but the event or symptom is easily tolerated (e.g., no reduction in daily activities is required).
Moderate:	The participant experiences sufficient discomfort to interfere with or reduces their usual level of activity.
Severe:	Significant impairment of functioning: the participant is unable to carry out usual activities and/or the participant's life is at risk from the event.
Life-Threatening:	The participant is at significant risk of life; it does not refer to an event which hypothetically might have caused death if it were more severe (life-threatening consequences, urgent intervention required).
Death:	Death related to an event.

Assessment of causality

We will utilise recommendations from the Council for International Organisations of Medical Sciences (CIOMS VI) to incorporate medical history, lack of efficacy/worsening of existing condition, trial and other medications and procedures into causality assessment of an AE/SAE using following terminologies: i) Not related - no reasonable possibility of causal relationship, and ii) Related - there is at least a reasonable possibility of a causal relationship between an adverse event and an investigational medicinal product. This means that there are facts (evidence) or arguments to suggest a causal relationship.

All AEs will be followed up until final outcome is known (i.e., outcome is assessed recovered/resolved, recovered with sequalae) or until the end of AE follow-up period. All SAEs will be followed up until final outcome is known (i.e., outcome is assessed as recovered, recovered with sequelae or death, or until the investigator assesses event as "chronic" or "stable"), the event is otherwise explained, or the participant is lost to follow-up.

Statistics and data analysis

This trial uses a rule-based design and has no formal sample size calculation. Non-evaluable participants will be replaced to ensure proper number of evaluable participants. For our primary analysis of the safety and tolerability of DNDi-6899, we will summarise all adverse events (AEs) or adverse reactions (ARs) and serious adverse events (SAEs) by cohort, and pooled. For Part A, the effect of food on the pharmacokinetics of DNDi-6899 will be examined. AUC(0-t), AUC(0-∞) and Cmax of DNDi-6899 will be analysed after a log transformation of the data. For Part B, dose proportionality will be assessed following single dose of DNDi-6899 via analyses of AUC(0-∞) and Cmax. Dose proportionality following repeated dosing will be assessed using AUC(0-tau), Cmax and Ctau. The analysis will be performed on log-transformed data. The extent of accumulation of DNDI-6899 will be based on AUC (RAUC(0-tau)), Cmax (RCmax) and Ctau (RCtau). The focus of the statistical analysis will be to estimate the accumulation ratio, Ro, on the pharmacokinetics of DNDI-6899.

Conclusions

Before DNDI-6899 can be assessed in a phase II efficacy trial, further information is needed on appropriate oral dose regimen. This phase I clinical trial will assess the safety and tolerability of escalating oral doses in fed and fasted states that offer consistent and safe plasma concentrations. It is anticipated that this trial will provide important information for developing a dose regimen that is safe and efficacious for a phase II trial in patients with Visceral Leishmaniasis.

Sponsor

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Data availability

All data will be made available in compliance with the DNDi policy on data sharing and secondary use of human subject research data.

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