CLINICAL TRIAL PROTOCOL SYNOPSIS

A RANDOMIZED, DOUBLE-BLIND (SPONSOR UNBLINDED), PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SINGLE DOSE IN FED STATE, AND REPEAT DOSES OF DNDI-6899 IN HEALTHY PARTICIPANTS

Name of product(s)	DNDI-6899
Drug Class	Inhibitor of Leishmania Cdc2-related kinase 12 (CRK12)
Phase	Phase I
Indication	Visceral Leishmaniasis (VL)
Protocol Number	DNDi-6899-01
Sponsor	DNDi, Chemin Camille Vidart, 15, 1202 GENEVA Switzerland Phone: +41 22 906 9230
Global/National Coordinating Investigator/Principal Investigator	
Clinical Trial Protocol Version / Date	V3.0 – Dated 19 December 2024.

Background Information and Trial Rationale	Introduction: Visceral leishmaniasis (VL) is a parasitic disease caused by obligate intracellular protozoan parasites, particularly by the species *Leishmania donovani* and *Leishmania infantum*. If left untreated, cases of VL are typically fatal. While therapies are available to treat the disease, none are ideal for use (due to toxicity, route of administration and cost) in resource poor settings where the disease is endemic. As such there is a real unmet medical need for new, short course oral drugs for the treatment of this disease. DNDI-6899, formerly known as [redacted], is a pyrazolopyrimidine derivative that is an inhibitor of *Leishmania* Cdc2-related kinase 12 (CRK12), with an antiparasitic effect, indicated for the treatment of visceral leishmaniasis. Results of Single Ascending Dose study: [redacted] conducted the early development of this DNDI-6899 and were the sponsor for the First-In-Man study. The First-in-Human study was conducted at one centre in UK with first participant first visit on 30 April 2019 and last participant last visit completed on 07 January 2020. This study was single ascending, randomised, 4-way cross over design conducted in 2 cohorts under fasting conditions in healthy participants. the Single Ascending Dose part (Part A Cohorts 1 and 2) of this study to receive DNDI-6899 or placebo. One participant who was inadvertently randomized to the study withdrew on the day of randomization, prior to dosing. The DNDI-6899 doses assessed in Part A were 30 mg, 60 mg, 120 mg, 300 mg, 600 mg, and 800 mg. All participants were males, and a majority of the participants were of White/Caucasian or European heritage. Of the 24 participants included in the safety population, 16 (67%) completed the study and 8 (33%) were withdrawn; none of them withdrew due to serious or drug-related safety reasons. No SAEs or other significant AEs were reported during the study. One participant discontinued the study due to an AE of abdominal discomfort; the event was of mild severity and not considered related to the study treatment by the investigator. No clinically significant changes were observed in ECG findings during the study. Good safety and tolerability were observed up to the highest single dose of 800 mg. DNDI-6899 was rapidly absorbed following single dose administration of 30 mg to 800 mg, with exposure increasing in a slightly more than dose proportional manner across the range studied. The elimination half-life was approximately 2 to 5 hours for the 30 mg to 800 mg dose range. Rationale for Multiple Ascending Dose and Food Effect study: This study was placed on a temporary halt after completion of the Single Ascending Dose part (part A, cohorts 1 and 2), but before the evaluation of the food effect (Part A, cohort 3) and the Multiple Ascending Dose part (Part B). Following the clinical hold, [redacted] terminated their involvement in the development of the product in 2021 and transferred the rights to continue development to DNDi. DNDi will be the sponsor for subsequent clinical studies with DNDI-6899.

The DNDi-6899-01 study will re-start the clinical investigation in humans with the Food Effect part and the Multiple Ascending Dose part in healthy participants. The study will be performed at single centre in an MHRA-accredited Phase I unit in the UK.

Rationale for dose selection

Dose selection was based on in silico modelling using the results from the SAD study and non-clinical studies, described in the [redacted] PK report dated 19 March 2019 prepared to support dose decision for MAD and FE evaluations.

- Food Effect part

Power model calculations performed by [redacted] in the SAD study predicted a marginal decrease in the DNDI-6899 exposure when taken with food. This could possibly be attributed to higher drug solubility in the fasted stomach than in the fed state, when the gastric pH is higher. Hence it is expected that the exposure in the presence of food will be similar to or slightly lower than in the fasted state. Based on this, the dose for the food effect part has been selected to be 350 mg, the maximum dose to be used in the MAD part as described below.

- Multiple Ascending Dose part

The SAD study showed that the half-life is 2-3 hours at doses <600 mg. Since no accumulation is expected with dosing every 12 hours, the exposure estimation for the MAD is based directly on the exposures seen in the SAD study. DNDI-6899 will be dosed twice-daily (BID).

The top dose in the MAD has been selected based on an assessment of the safety margin relative to the exposure at the NOAEL in the 28-day toxicology study in female rats, the most sensitive species (C_{max} 46.2 µg/mL and $AUC_{0\text{-}12h}$ 217 µg.h/mL). Based on modelling of the SAD data, 95% of humans would have a safety margin of at least 3.3-fold relative to this exposure with dosing of 500 mg BID (mean $AUC_{0\text{-}12h}$ 37.2 µg.h/mL, 95th percentile 65.0 µg.h/mL). The safety margin relative to C_{max} at this dose would be at least 5.3-fold for 95% of participants (mean C_{max} 5.53 µg.h/mL, 95th percentile 8.79 µg.h/mL).

BID dosing of 500 mg would also be expected to be sufficient to demonstrate efficacy. Efficacy in a BalbC mouse model of visceral leishmaniasis was demonstrated after 10 days treatment with DNDI-6899 at a dose of 25 mg/kg BID. This gave a whole blood exposure [approx. $AUC_{0\text{-}12h}$] of 7.632 µg.h/mL, corresponding to plasma $AUC_{0\text{-}12h}$ of 12.745 µg.h/mL. From the modelling, 95% of humans would have DNDI-6899 exposure of at least 1.6 times this value with dosing of 500 mg BID (5th percentile $AUC_{0\text{-}12h}$ 20.8 µg.h/mL).

Based on these results, 500 mg BID has been selected as the top dose for the MAD part of the study. 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 study conduct based on emerging data.

Dose Mg	**AUC_{0-12h}** µg.h/mL	**Dose multiple**	**AUC_{0-12h} multiple**
150	7.1		
300	18.0	2.00	2.54
500	37.2	1.67	2.07

Since this study is being conducted in health volunteers with appropriate safety monitoring, PK stopping criteria have been set based on a three-fold safety margin from the corresponding values at the NOAEL in female rats. These values (C_{max} 15.4 µg/mL, AUC_{0-12h} 72.3 µg.h/mL) will not be intentionally exceeded.

TABLE OF OBJECTIVES, ENDPOINTS AND KEY ESTIMANDS

OBJECTIVES	ENDPOINTS	KEY ESTIMANDS
PRIMARY:		
To evaluate the safety and tolerability of single and repeat doses of DNDI-6899 in healthy participants.	Adverse events, clinically significant abnormal laboratory values, vital signs, 12 lead electrocardiogram (ECG) findings, and 24 hours (hr) telemetry and Holter findings, and physical examination findings.	**Population:** Healthy adults in the safety analysis set. **Treatment condition:** Part A (Food Effect): Single dose of 500 mg of DNDI-6899 under fasted vs fed conditions. Part B (MAD): Three different doses of DNDI-6899 (150 mg, projected 300 mg, projected 500 mg) administered twice daily (BID) vs Placebo administered twice daily (BID) for 9 days and administered once in the morning on Day 10. **Intercurrent Events:** Participant withdrawal Incomplete dosing. **Strategy:** Data will be reported as captured. **Summary measure:** Categorical measurement - frequency and percentages for AEs, clinically significant abnormal laboratory values ECG, Holter and telemetry findings (by visit and relative time). Continuous measurement - Vital Signs ECGs and Labs: Mean and Median (by visit and

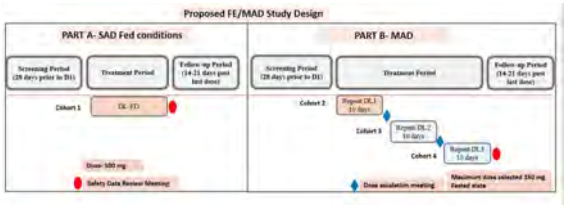
OBJECTIVES	ENDPOINTS	KEY ESTIMANDS
		relative time).
SECONDARY:		
To evaluate the systemic PK profile of single dose of DNDI-6899 under fasted and fed conditions and repeat doses of DNDI-6899 in healthy participants.	Plasma concentrations of DNDI-6899 plus derived parameters, as data allow. For Food 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.	**Population:** Healthy adults in the PK analysis set **Treatment condition:** Part A (Food Effect): Single dose of 500 mg of DNDI-6899 under fasted vs fed conditions. Part B (MAD): Three different doses of DNDI-6899 (150 mg, projected 300 mg, projected 500 mg) administered twice daily (BID) for 9 days and administered once in the morning on Day 10. **Intercurrent Events:** Participant withdrawal Incomplete dosing for the multiple ascending dose part or fed/fasted part **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 19 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,

OBJECTIVES	ENDPOINTS	KEY ESTIMANDS
		median of Tmax and arithmetic mean of T1/2.
To examine the food effect of DNDI-6899.	Food effect assessment using derived PK parameters^: AUC(0-t), AUC(0-∞),Cmax, T1/2 and Tmax	**Population:** Healthy adults in the PK analysis set **Treatment condition:** Part A (Food Effect): Single dose of 500 mg of DNDI-6899 under fasted vs fed conditions. **Intercurrent Events:** Participant withdrawal Incomplete dosing **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:** geometric mean ratios fed:fasted for AUC(0-t), AUC(0-∞) and Cmax Depending on data distribution, non-parametric or parametric statistical test for Tmax.
To examine dose proportionality following multiple doses of DNDI-6899.	Dose-proportionality assessment using derived PK parameters^: Day 1: AUC(0-tau), Cmax. Day 10: AUC(0-tau), Cmax, Ctau.	**Population:** Healthy adults in the PK analysis set **Treatment condition:** Part B (MAD): Three different doses of DNDI-6899 (150 mg, projected 300 mg, projected 500 mg) administered twice daily (BID) for 9 days and administered once in the morning on day 10. **Intercurrent Events:** Participant withdrawal Incomplete dosing **Strategy:** Data will be reported based on complete dosing and PK parameters from Day 10. That is,

OBJECTIVES	ENDPOINTS	KEY ESTIMANDS
		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- ∞) and Cmax across the 3 dose levels at Day 1. AUC(0-tau), Ctau and Cmax across the 3 dose levels at Day 10.
To assess 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.	**Population:** Healthy adults in the PK analysis set **Treatment condition:** Part B (MAD): Three different doses of DNDI-6899 (150 mg, projected 300 mg, projected 500 mg) administered twice -daily (BID) for 9 days and administered once in the morning on day 10. **Intercurrent Events:** Participant withdrawal Incomplete dosing **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.

OBJECTIVES	ENDPOINTS	KEY ESTIMANDS
EXPLORATORY:		
To assess urinary metabolites	Urine samples will be collected for analysis of metabolites of DNDI-6899	
To assess the effect of DNDI-6899 on Holter electrocardiogram parameters.	24 hour/48 hours Holter ECG will be recorded at regular intervals during the trial and analysed centrally	
To investigate any potential changes to exploratory renal biomarkers	Renal toxicity markers will be collected at regular intervals and analysed at the end of the trial	
To assess variation of mRNA expression in full blood before and after exposure to the drug (Transcriptional Profiling) for Part B (MAD) only	Variation of mRNA expression in blood sample before and after exposure to the drug (Transcriptional Profiling)	

* Accumulation ratios calculated as the ratio of geometric mean of the PK parameters on Day 10 to the geometric mean of Day 1 PK parameters: RAUC(0-tau) = geometric mean of all AUC(0-tau) on Day 10 to geometric mean of all AUC(0-tau) on Day 1, RCmax = geometric mean of all Cmax on Day 10 to geometric mean of all Cmax on Day 1, RCtau=geometric mean of all Ctau on Day 10 to geometric mean of all Ctau on Day 1. ^Do not have an occurrence of vomiting, diarrhoea, or concomitant medication use (that occurs at or before 2 times median Tmax within the appropriate treatment) or missing concentrations which render the concentration profile unreliable.

Trial Design	This study will be a randomized, double-blind (sponsor unblinded), placebo-controlled (only for part B), 2-part study of the oral administration of DNDI-6899 in healthy participants. This study is planned to ensure that a target of 36 evaluable participants will be randomized and will consist of 2 parts: • Part A (Food Effect part): 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 dose of DNDI-6899, previously selected from SAD study 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. Blood samples will be collected under both fed and fasted conditions for the analysis of DNDI-6899 and any metabolites. • Part B (Multiple Ascending Dose part): 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 randomized in a 3:1 ratio to receive repeat doses of either DNDI-6899 or placebo, according to the randomization schedule in a blinded manner. DNDI-6899 or placebo will be administered twice-daily (BID) dosing with a 12 hour dosing interval. Participants will receive each dose in fasted conditions. Depending upon the interim results from Part A in fasted conditions, it may be decided to dose DNDI-6899 and placebo in fed conditions. As Part B will be the first time DNDI-6899 is administered to humans as twice-daily dosing on successive days, the study design and especially the dose of the intermediate cohort (cohort 3) will be decided during study conduct based on emerging data as the study progresses. Between each cohort of Part B, the Dose Escalation Review Committee (DERC) will review and evaluate the interim safety, tolerability and PK data of the cohort, and the decision to escalate to the next cohort will be decided during DERC meeting with the Principal Investigator. A DERC Charter will be prepared accordingly to detail this process for Part B data review. The DERC will also review the data at the end of Part A before progression to part B. All participants in the study will attend a screening visit within 28 days prior to their first dose and a follow-up visit 14-21 days after their final dose. 

Main Entry Criteria Inclusion Exclusion	A sufficient number of participants will be screened to ensure that a target of 36 evaluable participants will be randomized (target Part A: 12 evaluable participants; Part B: 8 evaluable participants into each of 3 Cohorts). A participant is 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 study cannot participate in Part B. If participants prematurely discontinue the study, then additional replacement participants may be recruited and assigned to the same treatment sequence, at the discretion of the Sponsor in consultation with the Principal Investigator, in both Parts A and B. 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 contraception) 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.
	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, which must be at least 28 days prior to first dose of trial medication). Prescription medicine during the 14 days before the first dose of trial medication or use of an over-the-counter 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

<table>
<tr><td></td><td>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.</td></tr>
<tr><td>Study Duration</td><td>All screening assessments will be completed within 28 days prior to first-dose.

<u>Treatment duration for the Food Effect part</u>:
This will comprise of 2 treatment periods, investigating 2 dosing regimens under fasted and fed conditions. Each period will consist of a single dose given on Day 1, with participants in-house for 4 nights and 5 days. Participants will be admitted to the unit the day before dosing (Day -1) and will remain in the unit until Day 4, when they will be discharged after completion of all assessments.
The wash-out period will be at least 10 days between doses for an individual participant.

<u>Treatment duration for the Multiple Ascending Dose part:</u>
Each Cohort will consist of a 10-day treatment duration (Days 1-10), with participants in-house for 14 nights and 15 days. Participants will be admitted to the unit on Day -2 and will remain in the unit until Day 13, when they will be discharged after completion of all assessments.

<u>Follow-up period</u>:
At least 14 days and no greater than 21 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.

<u>Total duration for either FE or MAD cohorts</u>: Approximately 8-9 weeks</td></tr>
<tr><td>Study treatments</td><td>
<table>
<tr><th>Product name</th><th>DNDI-6899 powder in bottle</th><th>Placebo</th></tr>
<tr><td>Formulation description</td><td>Amorphous spray-dried powder</td><td>Powder blend</td></tr>
<tr><td>Dosage form</td><td>Powder in bottle (Extemporaneous preparation)</td><td>Powder in bottle (Extemporaneous preparation)</td></tr>
<tr><td>Route of administration</td><td>Oral</td><td>Oral</td></tr>
<tr><td>Physical description</td><td>White to slightly coloured powder</td><td>White to off-white powder</td></tr>
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<u>Food Effect part</u>: Dose: 350 mg (1 day of treatment for fed regimen and 1 day of treatment for fasted regimen). 12 evaluable participants

<u>Multiple Ascending Dose part</u>
Dose Cohort 1: 150mg, 10 days of treatment, twice daily dosing (BID) administered using a 12hr dosing interval (6 participants active, 2 placebo)
Dose Cohort 2: 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)</td></tr>
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<tr><td></td><td>Dose Cohort 3: 500mg, 10 days of treatment, twice daily dosing (BID) administered using a 12hr dosing interval (6 participants active, 2 placebo)</td></tr>
<tr><td>Sample Size</td><td><u>Food Effect part</u>:
The sample size is 14 participants for the FE part.
The objective is to determine if DNDI-6899 has a food effect and estimate its magnitude. A maximum of 14 participants will be recruited with the aim of getting evaluable data from 12 participants.
A participant is considered evaluable if they complete both screening and the 2 treatment periods and have appropriate PK parameters.

<u>Multiple Ascending Dose part</u>
The sample size is 24 evaluable participants with 8 participants per cohort, with the aim of a minimum of 6 evaluable participants per cohort. Additional participants may be recruited as replacement for withdrawn participants.
A participant is considered evaluable if they complete both screening and the 10-day treatment period and have the appropriate PK parameters.</td></tr>
<tr><td>Study population definitions</td><td>
<table>
<tr><th>Population</th><th>Description</th></tr>
<tr><td>Screened</td><td>All participants who were screened for eligibility</td></tr>
<tr><td>Enrolled</td><td>All participants who passed screening and entered the study. Included are Randomized Participants
Note: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study</td></tr>
<tr><td>Safety</td><td>All randomized participants who received at least one dose of study treatment.</td></tr>
<tr><td>PK</td><td>All participants who received at least one dose of IMP, who had at least 1 non-missing PK assessment</td></tr>
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</td></tr>
<tr><td>Statistical Analysis</td><td>Food Effect part: 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 analyzed after a $\log_e$ transformation of the data. An analysis of variance model will be fitted along with 90% confidence intervals using a mixed effects model, with fed/fasted condition as a fixed effect and subject as a random effect. Point estimates and corresponding 90% confidence intervals will be constructed for the comparisons of interest of DNDi-6899 fed – DNDi-6899 fasted, using the residual variance. These will then be back-transformed to provide point estimates and corresponding 90% confidence intervals for the geometric mean ratios fed: fasted.
MAD part: Dose proportionality will be assessed following single doses of DNDi-6899 (SAD part) via analyses of AUC (0-∞) and Cmax. Dose proportionality following repeated dosing will be assessed using AUC (0-tau), Cmax and Ctau. A statistical analysis will be performed using the power model. The analysis will</td></tr>
</table>

	be performed on log_e-transformed data. For each of these parameters a mixed effects model will be fitted with log_e (dose) as a fixed effect and individual participant fitted as random effects. Estimates of the mean slopes of loge (dose) will be reported along with corresponding 90% confidence intervals (slope≈1 implies dose proportionality). 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. Following log_e-transformation, AUC (0- tau) on Day 1 and AUC(0-tau) on the day of last dose will be analysed by a mixed effect model, fitting fixed effect terms for dose, day, and day by dose interaction, and fitting subject as a random effect. For each dose, point estimates and 90% confidence intervals for the differences "Day 10 - Day 1" will be constructed using the appropriate error term. The point estimates and associated 90% confidence intervals will then be exponentially back-transformed to provide point and 90% confidence interval estimates for the ratios "Day 10: Day 1" for each active dose. If both the dose and day by dose interaction terms are not significant, a single point estimate and confidence interval pooled across all doses will also be constructed. RCmax and RCtau will be estimated in a similar approach.

Table 1- Schedule of events: Food Effect part

Procedure	screening	Study period for each dose (fed and fasted)					Follow-up (14-21 days after last dose)	Notes
		D-1	D1	D2	D3	D4		
Outpatient Visit	x						x	
Admission to Clinical Unit		x						
Inpatient Stay at Clinical Unit		<<---------x---------->>						
Discharge from Clinical Unit						x		Following completion of all assessments.
Informed consent	x							
Inclusion and exclusion criteria	x							
Demography	x							
Full physical examination	x	x						Additional exams/screens may be performed by the Investigator, as deemed necessary. Tests will be conducted within site specified standards.
Brief physical examination				x		x	x	
Drug/Alcohol/Smoking Screen	x	x						Tests include alcohol breath test, smoking breath test and urine drug screen
Medical/Medication/Drug/Alcohol history	x							
Human immunodeficiency virus (HIV), Hepatitis B and C Screening	x							
Follicle stimulating hormone (FSH) + Oestradiol+ standard HCG pregnancy test	x							Females only, if required
Holter Monitoring (48 hours)	x	<< -----x------>>						
Haematology/ Clinical Chemistry /Urinalysis Test (Include Liver Chemistries)	x	x		x		x	x	If trace protein in urine is detected, a repeat test can be performed (within 24 hours). If tests are considered abnormal, further quantification is required. Non-fasted samples can be collected on Day -1 and the Follow-Up Visit. All other samples to be collected in a fasted state

Procedure	**screening**	**Study period for each dose (fed and fasted)**					**Follow -up (14-21 days after last dose)**	**Notes**
		D-1	D1	D2	D3	D4		
Urine Sampling (metabolism)			X	x				A urine sample will be taken pre-dose on Day 1 (approx. 20mL) Then, all urine from each participant will be collected from 0-24 hrs post dosing
Safety biomarkers (KIM1, NGAL, Urinary albumin)			X	x				First urine sample of the morning to be collected (Day 1 sample collection should be pre-dose). Additional samples may be collected, as deemed necessary by the Investigator.
PK Blood Sampling			X	x				PK blood samples to be taken pre-dose on Day 1 and then at the following time points post first-dose: 10min, 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr, 8hr, 10hr, 12hr; 24hr. Blood volumes to be collected include 2 mL for all time-points from pre-dose to 10hrs, and 5 mL for time-points 12hr and 24 hr.
12-Lead ECG	x	x	T	x	<-x->			12-Lead ECG and Vital Signs to be conducted on Day -1 and pre-dose on Day 1 and then at the subsequent time points post-dose on D ay 1: 30 min, 1hr, 1.5hr, 2hr, 2.5hr, 4hr, 8hs, 12hr. Then, pre-dose and post-dose on Day 2, Day 3, Day 4 BP will be measured in both a supine (measured after 10 minutes rest in supine) and standing position T=triplicate
Vital Signs: heart rate (HR), blood pressure (BP), temperature and respiration rate	x	x	T	x	<-x->		x	
Telemetry			<-x->					Continuous at least 24hr post-dose. Initiate at least 15 min. prior to dosing
Meals		x	X	x	x	x		Fasting regimen: On Day 1, participants will have fasted 8hr overnight prior to dosing. An adapted standard breakfast will be served approximately 3hrs after dosing. Water permitted on an ad lib basis up to 1hr before dosing. No water to be taken in the hour prior to dosing except for the liquid part of the adapted standard breakfast for the Fed regimen. At least 8 fl oz (240ml) to be taken 1hr after dosing. No water to be taken in the hour after dosing except for the rinse of the dose
Randomization			X					
Study Treatment			X					
AE review	x	<<--------x-------->>					x	
SAE review	x	<<--------x-------->>					x	
Concomitant medication review	x	<<--------x-------->>					x	

Table 2 - Schedule of events: Multiple Ascending Dose part

Procedure	screening	Study period (Days)														Follow-up (14-21 days after last dose)	Notes
		-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	
Outpatient Visit	x																x	
Admission to Clinical Unit		x																
Inpatient Stay at Clinical Unit		<<----------x----------->>																
Discharge from Clinical Unit																x		Following completion of all assessments.
Informed consent	x																	
Inclusion and exclusion criteria	x																	
Demography	x																	
Full physical examination	x																	Additional exams/screens may be performed by the Investigator, as deemed necessary. Tests will be conducted within site specified standards.
Brief physical examination			x		X					x						x	x	Brief physical examination includes non-invasive visual acuity assessments using the Snellen chart.
Drug/Alcohol/Smoking Screen	x		x															Tests include alcohol breath test, smoking breath test and urine drug screen
Medical/Medication/Drug/Alcohol history	x																	
Human immunodeficiency virus (HIV), Hepatitis B and C Screening	x																	
Follicle stimulating hormone (FSH) + Oestradiol+ standard HCG pregnancy test	x																	Females only, if required
Holter Monitoring (48 hours)	x																	

Procedure	**screening**	**Study period (Days)**														**Follow-up (14-21 days after last dose)**	**Notes**
		-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	
Haematology/ Clinical Chemistry /Urinalysis Test (Include Liver Chemistries)	x		x		X		x		x		x		x		x	x	x	If trace protein is detected, a repeat test can be performed. Sample to be drawn pre -dose on Days 2, 4, 6, 8 and 10. Non-fasted samples can be collected on Day -1 and the Follow-Up Visit. All other samples to be collected in a fasted state
Cortisol test			x											x				Tests to be performed in the early morning on Day -1 and Day 11. If levels are <420nmol/L, then a adrenocorticotropic hormone (ACTH) stimulation test will be performed to assess hypothalamic pituitary adrenal (HPA) axis
Safety biomarkers x` (KIM1, NGAL, Urinary albumin)			x	x				x										Pre-dose urine sample at D1 of the morning to be collected. Samples to be collected in fasting conditions. Additional samples may be collected, as deemed necessary by the Investigator.
Telemetry				x	X													Continuous at least 24 hr post -evening dose. Initiate at least 15 min. prior to dosing
Randomization				x														
Study Treatment				x	X	x	x	x	x	x	x	x	x					BID dosing: DNDI-6899 or placebo will be administered using a 12hr dosing interval.
12-Lead ECG	x		x	T	X		x		x		x		x		x	x	x	T=triplicate 12-Lead ECG and Vital Signs to be conducted on Day-1 and pre-dose Day 1 and then at the subsequent time points post first-dose: 30 min, 1 hr, 1.5hr, 2hr, 2.5hr, 4hr, 6hr, 13hr and 14hr For Days 2-10: pre-dose assessments only. BP will be measured triplicate at baseline and single supine and single standing at various timepoints
Vital Signs: heart rate (HR), blood pressure (BP), temperature and respiration rate	x		x	T	X	x	x	x	x	x	x	x	x	x	x	x	x	

Procedure	**screening**	**Study period (Days)**														**Follow-up (14-21 days after last dose)**	**Notes**
		-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	
Urine Sampling (metabolite)													x	x				A urine sample will be taken pre-dose (approx. 20mL). All urine from each participant will be collected from 0-24 hrs post dosing
Meals			x	x	X	x	x	x	x	x	x	x	x	x	x	x		On Day 1 through to D10, participants will have fasted 8hr overnight prior to dose 1. A breakfast will be served approximately 2hr after dose 1. Dinner will be served at least 2hr prior to dose 2. A snack may be consumed approximately 2hr after dose 2. Standardized meals will be served as per the site schedule on Days -1 and Days 11-13. Water permitted on an ad lib basis up to 1hr before dosing. No water to be taken in the hour prior to dosing . At least 8 fl oz (240ml) to be taken 1 hour after dosing No water to be taken in the hour after dosing except for the rinse of the dose
PK sampling				<<----------x----------->>														PK samples will be collected pre-dose and at the following time points post first dose: Day 1: 10min, 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr, 8hr, 10hr, and 12hr Days 2 – 9: Pre-dose PK samples collected for each dose Day 10: PK samples will be collected pre-dose and at the following time points post first-dose: 10min, 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr, 8hr, 10hr, and 12hr. Day 11: 24hr sample post-dose from Day 10. Blood volumes to be collected include: • 2 mL for post first-dose 0-11 hrs, and • 5 mL for post first-dose 12-24 hrs (Days 1 and 10).
AE review	x	<<----------x----------->>															x	

Procedure	**screening**	**Study period (Days)**														**Follow-up (14-21 days after last dose)**	**Notes**
		-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	
SAE review	x	<<----------x----------->>														x	
Concomitant medication review	x	<<----------x----------->>														x	

Planning Information

Study Timelines

Final protocol available	December 2023
Study treatment supply available	January 2025
FSFV	March/April 2025
Duration of recruitment period	9 months
Duration of follow-up period (if applicable)	14 days
LSLV	Q4 20245
Interim analysis	NA
Final study report	Q1 2026

STUDY SCOPE

Target countries	UK (for consistency with the original [redacted] study that was approved by MHRA and conducted in the UK)
Enrollment target	36 evaluable participants: • 12 evaluable participants for the FE part • 24 evaluable participants for the MAD part
Number of sites	1 site - Phase I Unit
Number of participants per site	36 evaluable participants /site
DSMB involvement	No DSMB but Dose Escalation Review Committee is included in the study for dose escalation process between the cohorts of MAD part.
Partners involvement	NA
Other study special needs	NA

Study Treatments Supply

Study treatments	1. DNDI-6899 powder in bottle (33.3% w/w of DNDI-6899) DNDI-6899 spray-dried dispersion intermediate will be supplied in bulk to the clinical trial site for extemporaneous preparation of DNDI-6899 powder in bottle. 2. Placebo to match DNDI-6899 powder in bottle Placebo to match DNDI-6899 spray-dried dispersion intermediate will be supplied in bulk to the clinical trial site for extemporaneous preparation of placebo to match DNDI-6899 powder in bottle. DNDI-6899 spray-dried dispersion intermediate and placebo to match DNDI-6899 spray-dried dispersion intermediate will be manufactured at: [redacted]
Labeling instructions	The labels of the study treatments will contain following information: 1. Drug name 2. Dosage form and strength 3. Batch number 4. Route of administration 5. Clinical trial reference number 6. Name, address, and contact number of the sponsor 7. Name and contact number of the principal investigator 8. Storage condition and restriction 9. Expiry date 10. Statement - “For clinical trial use only”
Other information	1. DNDI-6899 powder in bottle will be reconstituted with 10% (v/v) propylene glycol in water-for-injection for immediate oral administration. 2. Placebo (white) to "match" DNDI-6899 powder (yellow) in bottle will be reconstituted with 10% (v/v) propylene glycol in water-for-injection for immediate oral administration.