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A study to investigate the safety, tolerability and activity of multiple ascending doses of DNDI-0690 in healthy volunteers including assessment of heart and kidney function

Submission date
12/01/2021

Recruitment status
No longer recruiting

Registration date
25/01/2021

Overall study status
Completed

Last Edited
13/03/2023

Condition category
Other

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The study sponsor (Drugs for Neglected Diseases initiative (DNDi)) is developing DNDI-0690 for the treatment of a disease called leishmaniasis. This disease is caused by a parasite (an organism which lives on or in another organism and uses the host to survive) which infects the body of female sandflies. These types of fly bite humans, and this causes the parasite to be passed on and infect a human host. This disease is commonly found in countries which are less developed with high rates of poverty, malnutrition and poor housing conditions. There are three main forms of the disease which can cause symptoms ranging from simple ulcer(s) in the skin, lesions affecting tissues in the mouth, nose and throat to the more complicated form presenting with fever, anaemia, weakness and weight loss which can be fatal if left untreated. Currently, there are treatment options available for this disease, but these are not the most effective as they require a long duration of treatment, most of them are given as an injection (in the muscle or veins), are associated with a number of side effects and are generally not effective against all forms of the disease. Therefore, there is an unmet need to develop potential new treatments with oral treatments which could be more effective, and which could be used to combat all forms of leishmaniasis in the areas affected by the disease.
The aim of this study is to investigate the study drug DNDI-0690. The main objectives of this study are as follows:
• To determine the safety and tolerability (the degree to which side effects of a drug can be tolerated) of DNDI-0690 when it is administered as multiple doses at different dose strengths over a period of up to 10 days.
• To investigate the concentration of DNDI-0690 in the blood and urine, and how this changes over a period of time
As well as evaluating the above, the researchers will also investigate the by-products of DNDI-0690 (known as metabolites) which are produced when DNDI-0690 is broken down in the body, and analyse the levels of biomarkers in the body. Biomarkers are markers within the body such as a gene, molecule or characteristic which can be used to identify the presence of a particular biological process occurring in the body or a particular disease. In addition, the researchers will

also assess variations in the levels of certain molecules in the body before and after exposure to the study drug. This will be performed by analysing a molecule in the body called mRNA (messenger RNA) which is responsible for producing the genetic code which makes proteins in the body. This investigation will apply to certain groups only.

Who can participate?
All participants must comply with the study entry and exclusion criteria. The most important entry criteria are:
1. Healthy male or female (of non-childbearing potential i.e. permanently sterilised or post-menopausal) between 18 and 55 years of age
2. Not taking any medication. Those who take medication should inform the study doctor as they may still be able to take part in the study if the medication will not interfere with the study drug.
3. Non-smoker who has not smoked for at least 12 months before the screening visit and has not used any nicotine replacement therapies such as gums, patches or e-cigarettes within the last 12 months.
4. Does not consume more than 6 cups of coffee or equivalent per day.

What does the study involve?
In this study, participants will either be given DNDI-0690 in the form of an oral capsule (multiple capsules per dose) or a placebo (which contains no active drug). Blood and urine samples will be taken at set time points throughout the study in order to measure the concentration profile of DNDI-0690 in the blood and urine, how this changes over time, and for the monitoring of heart and kidney function. The researchers will compare the results from each of the groups and each study part to determine if there are any significant differences in the safety profile of DNDI-0690, the concentration of DNDI-0690 in the blood and urine and how this changes over time or the effect on heart and kidney function. The purpose of the data generated in this study is to provide further information and guidance to support the study sponsor in the development of the study drug.

What are the possible benefits and risks of participating?
Taking part in this study is not expected to provide any direct medical benefit. However, the information from this study may help improve the treatment of leishmaniasis. Risks associated with the trial participation are mainly drug side effects and inconveniences linked to study procedures. They are all described in the study Participant Information Sheet which can be consulted on this website.

Where is the study run from?
Simbec-Orion Clinical Pharmacology (UK)

When is the study starting and how long is it expected to run for?
March 2020 to October 2021

Who is funding the study?
Wellcome Trust (UK) (grant number 212346/Z/18/Z - 21st Century Treatments for Sustainable Elimination of Leishmaniasis)

Who is the main contact?
Severine Blesson
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Contact information

Type(s)
Scientific

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Clinical Trials Information System (CTIS)
2020-003963-24

Integrated Research Application System (IRAS)
288914

Protocol serial number
DNDi069002 / RD 777/34920 /

Study information

Scientific Title
A Phase I, double-blind, randomised, single-centre, parallel-group, multiple-dose, dose-escalation, placebo-controlled study of the safety, tolerability and pharmacokinetics of DNDI-0690 after oral dosing in healthy subjects

Study objectives
DNDI-0690 is safe to be dosed in humans and provides sufficient exposure in healthy volunteers to be further investigated to treat visceral and cutaneous leishmaniasis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 02/11/2020, Wales Research Ethics Committee 1, Cardiff (Health and Care Research Wales, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; +44 (0)2920 785738; Wales.REC1@wales.nhs.uk), REC ref: 20/WA/0258

Primary study design
Interventional

Study design

Double-blind randomized single-centre parallel-group multiple-dose dose-escalation placebo-controlled study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
The safety, tolerability and fluid exposure of a drug aimed to treat visceral and cutaneous leishmaniasis in healthy volunteers

Interventions
The study will be conducted in three parts (Part A, Part B and Part C).

Part A: Multiple Ascending Dose Cohorts (Cohorts 1-4)
Part A will consist of up to four cohorts of nine subjects. Subjects will be randomly assigned to receive an oral dose of active IMP (six subjects) or matching placebo (three subjects) for 10 days in a sequential escalating manner with a minimum of 7 days interval between two cohorts.
In Part A, each cohort will follow a sentinel dose-escalation schedule; two subjects will be dosed on the first dosing day of each cohort (1 subject on active IMP and 1 subject on matching placebo). The remainder of the cohort (five subjects on active IMP and two subjects on matching placebo) will be dosed a minimum of 48 hours later pending confirmation of an acceptable safety profile in the dose-leader cohort by the Principal Investigator (PI), or medically-qualified designees who are familiar with the study protocol and Investigator's Brochure (IB).
The planned starting dose for Cohort 1 is 400 mg of DNDI-0690 once a day for 10 days. Doses to be administered in Cohorts 2 to 4 will be determined based on emerging PK and safety data. The number of daily doses may be increased to 2 by the implementation of a twice a day (BID) dosing regimen if the number of capsules in a single intake is raising concerns of acceptability. This decision will be made by the Safety Review Committee (SRC) prior to each cohort and will apply to all subjects within a cohort.

Part B: Cardiac pharmacodynamic assessment (Cohort 5 - Optional)
Part B will consist of one cohort of nine subjects. Subjects will be randomly assigned to receive an oral dose of active IMP (six subjects) or matching placebo (three subjects) for 5 days. Part B will only be implemented if the SRC considers it safe and appropriate to proceed with a maximum considered dose of 3600 mg. This cohort is thus considered optional.
Subjects in Part B will follow a sentinel schedule; two subjects will be dosed on the first dosing day (one subject on active IMP and one subject on matching placebo). The remainder of the cohort (five subjects on active IMP and 2 subjects on matching placebo) will be dosed a minimum of at least 48 hours later pending confirmation of an acceptable safety profile in the dose-leader cohort by the PI, or medically-qualified designees who are familiar with the study protocol and IB.

Part C: Measured Glomerular Filtration Rate (mGFR) Cohort (Cohort 6)
Part C will consist of one cohort of nine subjects.
Subjects will be administered DNDI-0690 or placebo once daily for 10 days at a dose level that is either at or below the highest well-tolerated dose of DNDI-0690 as evaluated in the Part A dose-escalating cohorts. The dose will be decided by the SRC after reviewing data from Part A. As this dose will already have been explored, no sentinel group will be implemented in this cohort.
All subjects will receive 5 ml of iohexol solution (300 mg/mL iodine) intravenously on Day -1, Day 10, and optionally Day 24-28 that will be flushed with 10 ml of normal saline solution. On Day -1,

iohexol will be administered at the same time as expected dosing of the study drug or placebo on Day 10. On Day 10, iohexol will be administered immediately after dosing of study drug or placebo.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
DNDI-0690 nitroimidazooxazine

Primary outcome(s)
Part A & B:
Safety and tolerability of DNDI0690 after multiple oral doses in fasted conditions measured by:
1. Frequency of adverse events (AEs), based on the clinical judgement of the investigator, occurring from first dosing up to post-study follow-up visit (14 to 18 days post last dose)
2. Frequency of participants reporting AEs, based on the clinical judgement of the investigator, from first dosing up to post-study follow-up visit (14 to 18 days post last dose)
3. Causality of AEs based on the clinical judgement of the investigator, occurring from first dosing up to post-study follow-up visit (14 to 18 days post last dose)
The possible relationship between the AE and the study drug will be quoted as follows:
Not related: There is no reasonable possibility of a causal relationship.
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.
4. Severity of AEs assessed based on the clinical judgement of the investigator, occurring from first dosing up to post-study follow-up visit (14 to 18 days post last dose). The severity of the AEs will be determined in the following manner:
4.1. Mild: An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities
4.2. Moderate: An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed
4.3. Severe: An AE that prevents normal everyday activities; treatment or other intervention usually needed
4.4. Life-Threatening: The subject 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).
4.5. Death: Death related to an event.

Part C:
Glomerular filtration rate (GFR) calculated from iohexol clearance before (D-1) and after administration of DNDI-0690 (D10) in healthy subjects in fasted condition at maximum well-tolerated dose tested in Part A or below

Key secondary outcome(s)
Part A&B:
1. AUC0-∞ (area under the plasma concentration-time curve from administration up to infinity with extrapolation of the terminal phase) calculated following quantification of DNDI-0690 by LC /MS-MS in plasma from last dosing up to 48 hours post dose

1. AUC0-24 (area under the plasma concentration-time curve from administration up to 24h post-dose) calculated following quantification of DNDI-0690 by LC/MS-MS in plasma on D1 and last day of dosing
2. Cmax (observed maximum plasma concentration) calculated following quantification of DNDI-0690 by LC/MS-MS in plasma on D1 and last day of dosing
3. Other PK descriptive parameters derived from quantification of DNDI-0690 in plasma and urine by LC/MS-MS from D1 up to 48 hours post dose
4. Cardiologic pharmacodynamics parameters of DNDI0690 measured from electrocardiograms (ECG) recordings extracted from Holter at baseline and on last day of dosing

Completion date
13/10/2021

Eligibility

Key inclusion criteria
1. Healthy males or healthy women of non-childbearing potential (WONCBP) between 18 and 55 years of age inclusive at the time of signing informed consent
2. Female subject of non-childbearing potential. WONCBP is defined as women who are postmenopausal or permanently sterilised (permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy)
3. Female post-menopausal state is defined as no menses for 12 months without an alternative medical cause and confirmed by a serum FSH result of ≥40 IU/L at Screening
4. Male subject (and subject's partner of childbearing potential) must use condom and also willing to use a highly effective method of contraception or 2 effective methods of contraception (see Section 10.5.2), if applicable (unless anatomically sterile or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the subject) from first dose until 3 months after last dose of IMP
5. Body mass index (BMI) of 18.0 to 30.1 kg/m2 as measured at Screening and body weight ≥60 kg (BMI = body weight (kg) / [height (m)]2)
6. No clinically significant abnormal test results for serum biochemistry, haematology and/or urine analyses within 28 days before the first dose administration of the IMP
7. Subject with a negative urinary drugs of abuse (DOA) screen (including alcohol and cotinine) test results, determined within 28 days before the first dose administration of the IMP (N.B.: A positive test result may be repeated at the Investigator's discretion)
8. Subject with negative human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg)) and hepatitis C virus antibody (HCV Ab) test results at Screening
9. General good physical health determined by medical and surgical history, physical examination, 12-lead ECG, vital signs and clinical laboratory tests
10. Normal blood pressure: systolic blood pressure between ≥90 and ≤140 mmHg, Diastolic blood pressure ≤90 mmHg, measured after 10 min rest in supine position at Screening, admission and pre-dose
11. A resting heart rate (HR) between ≥50 and ≤100 bpm measured after 10 min rest in supine position at Screening, admission and pre-dose
12. ECG recording without clinically significant abnormality, including QTcF measure of ≤450 msec at Screening, admission and pre-dose
13. No febrile seizures or infectious illness for at least 7 days prior to first administration of the IMP (Day 1)
14. Must agree to adhere to the contraception requirements and the life-style restrictions

15. Subject must be available to complete the study (including all follow-up visits)
16. Subject must satisfy an Investigator about his/her fitness to participate in the study
17. Subject must provide written informed consent to participate in the study

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
45

Key exclusion criteria
1. Subjects who have received any IMP in a clinical research study within 90 days prior to Day 1
2. Subjects who are study site employees, or immediate family members of a study site or sponsor employee
3. Subjects who have previously been enrolled in this study and/or have received DNDI 0690 previously
4. History of any drug or alcohol abuse in the past 2 years
5. Demonstrating excess in caffeine/xanthine consumption (more than 6 cups of coffee or equivalent a day)
6. Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = ½ pint beer, or a 25 ml shot of 40% spirit, 1.5 to 2 Units = 125 ml glass of wine, depending on type). As confirmed by a positive urine alcohol test at Screening or admission
7. Current smokers or those who have smoked within the last 12 months with a positive cotinine result at Screening and Admission
8. Current users of cigarette replacements (i.e. e-cigarettes, nicotine patches or gums) and those who have used these products within the last 12 months
9. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the Investigator or delegate at Screening
10. Clinically significant abnormal biochemistry, haematology, coagulation or urinalysis as judged by the Investigator or AST/ALT/total bilirubin/gamma-glutamyl transpeptidase [GGT]/ALP /creatinine >1.2 ULN. Subjects with Gilbert's syndrome are allowed
11. Positive PCR COVID-19 test at admission
12. Evidence of renal impairment at Screening or admission, as indicated by an estimated Glomerular Filtration Rate (GFR) <lower limit of normal (LLN) using the CKD-EPI equation
13. History of clinically significant cardiovascular, renal, hepatic, neurological (especially seizures), immunological, psychiatric, myopathies, bleeding tendency, respiratory and particularly gastrointestinal (GI) disease, especially peptic ulceration and chronic gastritis, GI bleeding, ulcerative colitis, Crohn's Disease or Irritable Bowel Syndrome, as judged by the Investigator

14. History of additional risk factors for Torsades des Pointe (i.e. heart failure, hypokalaemia, family history of long QT syndrome)
15. Rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency
16. Any relevant GI complaints within 7 days of dosing
17. Serious adverse reaction or clinically relevant hypersensitivity to any drug or the formulation excipients (Hypromellose [HPMC], sodium lauryl sulphate [SLS], sucrose, croscarmellose sodium and magnesium stearate)
18. Presence or history of clinically significant allergy requiring treatment (including asthma, urticaria, clinically significant allergic rash or other severe allergic diathesis), as judged by the Investigator. Hay fever is allowed unless it is active
19. Donation or loss of greater than 500 ml of blood within the previous 3 months or more than 100 ml within 30 days prior to signature of informed consent
20. Subjects who are taking, or have taken, any prescribed or over-the-counter drug (including anti-acid drugs) or vitamins/herbal remedies (i.e. St. John's Wort and others which are known to interfere with the CYP3A4 and P-gp metabolic pathways) or hormone replacement therapy (HRT) or any drug known to modify the MATE-1/OCT-2 renal transporters (such as, for example, cimetidine, ritonavir, trimethoprim, cisplatin) in the 28 days before IMP administration (or 5 half-lives of the taken drug, whichever is longer). Administration of up to 4 g of paracetamol per day within 7 days of IMP administration is allowed
21. Surgery within 12 weeks prior to Screening, with the exception of appendectomy
22. Any surgery (i.e. gastric bypass) or medical condition that may affect the absorption of orally administered drugs
23. Failure to satisfy the Investigator of fitness to participate for any other reason
24. Breastfeeding and lactating females

Date of first enrolment
20/12/2020

Date of final enrolment
16/06/2021

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre
Simbec-Orion Clinical Pharmacology
Merthyr Tydfil
United Kingdom
CF48 4DR

Sponsor information

Organisation
Drugs for Neglected Diseases Initiative

ROR
https://ror.org/01tp0e450

Funder(s)

Funder type
Research organisation

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Severine Blesson (sblesson@dndi.org). Scientific evaluation of requests will be performed internally by the Sponsor. Any data sharing will be conducted under strict compliance with EU GDPR regulation (and any UK equivalent). Please refer to the ICF provided for the extent of consent obtained from participants.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		13/03/2023	13/03/2023	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	version V3.0 version V3.0	14/12/2020	25/01/2021	No	Yes

Participant information sheet		14/12/2020	25/01/2021	No	Yes
Participant information sheet	version V3.0	14/12/2020	25/01/2021	No	Yes
Protocol file	version V3.0	07/12/2020	25/01/2021	No	No
Protocol file	version 5.0	27/08/2021	15/12/2022	No	No