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Study to test the safety and tolerability of a new drug (DNDI-0690) in healthy subjects

Submission date
14/03/2023

Recruitment status
No longer recruiting

Registration date
23/03/2023

Overall study status
Completed

Last Edited
06/04/2023

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
DNDi is developing a new medicine to treat leishmaniasis which is a tropical disease with a strong link to poverty. Leishmaniasis is spread by the bite of certain types of sand-flies. Cases have been recorded in 101 countries around the world and there are 350 million people at risk of getting the disease. Symptoms of the disease can range from skin ulcers, fever, and weight loss and can be fatal if left untreated.
Treatments that are currently available for Leishmaniasis are limited, can be toxic and require a stay in hospital lasting several weeks. They are also not easy to administer. For example, some treatments need to be given by an infusion into the vein, others require several injections per day in the muscles. DNDi is conducting this study to develop a safer, short-term treatment that can be given easily by mouth without the requirement for long stays in hospital.
We will be looking at how the test medicine is taken up and broken down by the body. We will also look at the safety and tolerability of the test medicine and we may look at how food affects the way the test medicine is taken up and broken down by the body.

Who can participate?
To participate, you must have between 18 and 55 years of age for males, between 18 and 60 years of age for females, be a healthy male or be a healthy female who is no longer able to have children (considered as non-childbearing potential);

What does the study involve?
In this study, participants will either be given DNDI-0690 in the form of an oral capsule (one or 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, and how this changes over time. The researchers will compare the results from each of the groups 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. 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 with 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?
Quotient Sciences, Nottingham, (UK)

When is the study starting and how long is it expected to run for?
April 2018 to December 2019

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
Severine Blesson
sblesson@dndi.org

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2018-002021-35

IRAS number

ClinicalTrials.gov number
NCT03929016

Secondary identifying numbers
DNDi-0690-01, WT 212346/Z/18/Z

Study information

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

Acronym
DNDi-0690-01

Study objectives
DNDI-0690 is safe to be dosed as a single dose 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 12/03/2019, London - Surrey Borders Research Ethics Committee (Health Research Authority, Skipton House, 80 London Road, London, SE1 6LH, UK; +44 207 104 8199; surreyborders.rec@hra.nhs.uk); ref: 19/LO/0373

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

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Pharmaceutical testing facility

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Visceral leishmaniasis, cutaneous leishmaniasis

Interventions
This is a single centre, double-blind, randomised, placebo-controlled, parallel-group, single oral dose, dose-escalation study in healthy male and women of non-childbearing potential (WONCBP) subjects. It is planned to enroll 8 subjects in 8 planned cohorts. Cohorts 1 to 7 will include male subjects. Cohort 8 will include WONCBP subjects.

Subjects will be randomly assigned using an online tool to receive a single oral dose of active investigational medicinal products (IMP - DNDI-0690) or a matching placebo in a sequential escalating manner with a minimum of 7 days between dosing of each cohort.

The planned starting dose for Cohort 1 (Regimen A) will be 10 mg of DNDI-0690. Doses to be administered in Cohorts 2 to 8 will be determined based on emerging PK and safety data.

Intervention Type
Drug

Phase
Phase I

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

Primary outcome measure
Occurrence of Treatment-emergent adverse events (TEAEs) from baseline up to 7-10 days post-dose

Secondary outcome measures
Measured by blood test:
1. Area Under the Plasma Concentration Versus Time Curve (AUC) From Zero Extrapolated to Infinity (AUC0-inf) from pre-dose up to 72 hours post-dose
2. Observed Maximum Concentration (Cmax) from pre-dose up to 72 hours post-dose
3. Time to Maximum Observed Plasma Concentration (Tmax) from pre-dose up to 72 hours post-dose
4. Apparent elimination half-life (T1/2) from pre-dose up to 72 hours post-dose

Overall study start date
01/04/2018

Completion date
06/12/2019

Eligibility

Key inclusion criteria
1. Healthy males (Cohorts 1 to 7) or healthy WONCBP (Cohort 8)
2. 18 to 55 years (Cohorts 1 to 7) or 18 to 60 years (Cohort 8) of age at the time of signing informed consent
3. Body mass index (BMI) of 18.0 to 30.1 kg/m² as measured at screening
4. General good physical health determined by medical and surgical history, physical examination, 12-lead ECG, vital signs and clinical laboratory tests
5. 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
6. A resting HR between ≥40 and ≤90 bpm measured after 10 min rest in supine position at screening, admission and pre-dose
7. ECG recording without clinically significant abnormality, including QTcF measure of ≤450 msec

(male) or ≤470 msec (female) at screening, admission and pre-dose
8. Having had no febrile seizures or infectious illness for at least 7 days prior to administration of the IMP (Day 1)
9. Must be willing and able to communicate and participate in the whole study
10. Must provide written informed consent
11. Must agree to adhere to the contraception requirements

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
64

Total final enrolment
64

Key exclusion criteria
1. Subjects who have received any IMP in a clinical research study within the 3 months or 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 alcohol breath test at screening or admission
7. Current smokers and those who have smoked within the last 12 months. As confirmed by a breath carbon monoxide reading of greater than 10 ppm at screening or admission
8. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months
9. Females of childbearing potential including those who are pregnant or lactating (all female subjects must have a negative serum pregnancy test at screening and admission). A woman is considered of childbearing potential unless she is permanently sterile (hysterectomy, bilateral salpingectomy, bilateral tubal ligation, bilateral tubal occlusion and bilateral oophorectomy) or is postmenopausal (had no menses for 12 months without an alternative medical cause and a serum follicle stimulating hormone [FSH] concentration ≥40 IU/L)
10. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator or delegate at screening
11. Clinically significant abnormal biochemistry, haematology, coagulation or urinalysis

(especially AST, ALT, gamma glutamyl transpeptidase [GGT], ALP, creatinine, and BUN) as judged by the investigator (laboratory parameters are listed in Appendix 1). Subjects with Gilbert's syndrome are allowed
12. Confirmed positive drugs of abuse test result (drugs of abuse tests are listed in Appendix 1)
13. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) results
14. Evidence of renal impairment at screening or admission, as indicated by an estimated CLcr of <80 mL/min using the Cockcroft-Gault equation
15. History of clinically significant cardiovascular, renal, hepatic, neurological (especially seizures), immunological, psychiatric, myopathies, bleeding tendency, respiratory and particularly GI disease, especially peptic ulceration and chronic gastritis, GI bleeding, ulcerative colitis, Crohn's Disease or Irritable Bowel Syndrome, as judged by the investigator
16. History of additional risk factors for Torsades des Pointe (eg heart failure, hypokalaemia, family history of long QT syndrome)
17. Rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency
18. Any relevant GI complaints within 7 days of dosing
19. Subjects with a history of cholecystectomy or gall stones (Cohort 7 only)
20. 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)
21. 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
22. Donation or loss of greater than 500 mL of blood within the previous 3 months or more than 100 mL within 30 days before signing ICF to this trial
23. Subjects who are taking, or have taken, any prescribed or over-the-counter drug (including anti-acid drugs) or vitamins/herbal remedies (eg St. John's Wort and others which are known to interfere with the CYP3A4 and P-gp metabolic pathways) or HRT in the 21 days before IMP administration. Administration of up to 4 g of paracetamol per day within 7 days of IMP administration is allowed
24. Surgery within 12 weeks prior to screening, with the exception of appendectomy
25. Any surgery (eg gastric bypass) or medical condition that may affect absorption of orally administered drugs
26. Failure to satisfy the investigator of fitness to participate for any other reason

Date of first enrolment
04/04/2019

Date of final enrolment
08/11/2019

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Quotient Sciences
Mere Way
Ruddington Fields
Ruddington
Nottingham
United Kingdom
NG11 6JS

Sponsor information

Organisation
Drugs for Neglected Diseases Initiative

Sponsor details
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Sponsor type
Charity

Website
https://dndi.org/

ROR
https://ror.org/022mz6y25

Funder(s)

Funder type
Charity

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

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
01/10/2023

Individual participant data (IPD) sharing plan
The datasets generated during the current study will be available upon request from Sponsor sblesson@dndi.org

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 5.0	23/10/2019	21/03/2023	No	Yes
Protocol file	version 3.0	04/09/2019	21/03/2023	No	No
Basic results			06/04/2023	No	No
HRA research summary			28/06/2023	No	No