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Study of first dosing of a new compound DNDi-6148 in healthy volunteers to assess safety and drug levels in blood and urine after escalating single dose

Submission date
26/06/2020

Recruitment status
No longer recruiting

Registration date
03/07/2020

Overall study status
Completed

Last Edited
27/06/2023

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
DNDI-6148 is a drug developed to treat visceral leishmaniasis (VL), a potentially lethal disease caused by the Leishmania parasite and transmitted by the female sandfly (small insects that are morphologically similar to mosquitoes). This disease is endemic in East Africa, the Indian Peninsula and South America, where it affects vulnerable populations. To a lesser degree, it also affects a few people in Southern Europe, mainly immunocompromised patients.
The main aim of this study is to assess the safety and tolerance of the DNDI-6148 product after giving increasingly large single doses to healthy male volunteers, compared to a placebo (a medication that is indistinguishable the product to be tested, but does not contain the active molecule). This study will also be used to study DNDI-6148's pharmacokinetic properties (the fate of the medication in the blood) and pharmacodynamic properties (the effect of the medication on the volunteer, more specifically on the electrocardiogram).

Who can participate?
Healthy men aged 18 to 50

What does the study involve?
A study check-up for the selection appointment (physical examination, electrocardiogram, blood tests, alcohol and drug screens), then 5 days of hospitalization in the clinical unit, including several check-ups and dosing of the drug once. Participants are randomly allocated to receive either the active drug or a placebo. A single dose of treatment will be given as an oral suspension (liquid) with increasing doses for each group of participants. The last follow up visit is 72 hours later. A maximum of 450 ml of blood will be drawn.

What are the possible benefits and risks of participating in the study?
No benefit for health can be expected for participants to the study and taking medication of any kind poses some risks linked to individual reactions, which are difficult to predict. Drawing blood can cause bruising, pain or bleeding and carry a low risk of infection. Since this is a study of the

first use of the product in humans, the adverse effects (frequent or not) of this medication have not yet been identified.

Where is the study run from?
Eurofins Optimed (France)

When is the study starting and how long is it expected to run for?
January 2018 to March 2022

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

Who is the main contact?
Sophie Delhomme
sdelhomme@dndi.org

Contact information

Type(s)
Scientific

Contact name
Ms Sophie Delhomme

Contact details
DNDi
15 Chemin Louis Dunant
Geneva
Switzerland
1202
+41 (0)22906 92 79
sdelhomme@dndi.org

Additional identifiers

Clinical Trials Information System (CTIS)
2018-004023-37

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
DNDi-6148-01 / OP105718.DND

Study information

Scientific Title

A Phase I, blinded, randomized, single-centre, parallel-group, single-dose, dose-escalation, placebo-controlled study of the safety, tolerability, and pharmacokinetics of DNDI-6148 after oral dosing in healthy male subjects

Study objectives
DNDI-6148 is safe to be dosed in humans and provides sufficient exposure in healthy volunteers to be further investigated to treat visceral leishmaniasis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/12/2018, Committee of people protection South-East and Overseas II (Comité de Protection des Personnes, Agence regionale de santé Occitanie, Bureau 1048, 10 chemin du raisin, 31050 Toulouse Cedex9, France; +33 (0)5 34 30 27 55; cppsoom2@ars.sante.fr), ref: 2-18-90 / SI 1823

Study design
Single-center interventional blinded randomized parallel-group single-dose dose-escalation placebo-controlled study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Treatment of visceral and/or cutaneous leishmaniasis

Interventions
Sixty-four (64) healthy male volunteers, aged 18 to 50 will be included in the study. Randomization is performed by block of 2 (1:1 for placebo:active) for the sentinel group, followed by block of 6 (1:5) for the main group of each dose cohort. A coding list was issued at the start of the trial, only available to unblinded personnel. Each cohort will include 8 participants (randomized in 6 active/2 placebo). A single dose of treatment will be administered as an oral suspension with increasing doses for each cohort of 8, such as 10 mg, 20 mg, 40 mg, 80 mg, 160 mg, 260 mg, 380 mg and 500 mg. The treatment will be administered as a single dose on Day 1. Last follow up visit is 72 h post-dosing.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
DNDI-6148

Primary outcome(s)

Safety and tolerability of DNDI6148 measured by:
1. Frequency of adverse events (AEs), based on the clinical judgement of the investigator, occurring from dosing up to 72 h post-dose
2. Frequency of participants reporting AEs, based on the clinical judgement of the investigator, from dosing up to 72 h post-dose
3. Causality of AEs based on the clinical judgement of the investigator, occurring from dosing up to 72 h post-dose, The possible relationship between the AE and the study drug will be quoted as following:
Not related: There is no reasonable possibility of 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 dosing up to 4 days post-dose, The severity of the AEs will be determined in the following manner:
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 his or her 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.

Key secondary outcome(s))
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-6148 by LC /MS-MS in plasma from dosing up to 72 hours post dose
2. Cmax (observed maximum plasma concentration) calculated following quantification of DNDI-6148 by LC/MS-MS in plasma from dosing up to 72 hours post dose
3. Other PK descriptive parameters derived from quantification of DNDI-6148 in plasma and urine by LC/MS-MS from dosing up to 72 hours post dose
4. Cardiologic pharmacodynamics parameters of DNDI6148 measured from electrocardiograms (ECG) recordings from baseline up to 72 hours post dose

Completion date
08/03/2022

Eligibility

Key inclusion criteria
1. Healthy Caucasian male volunteer aged 18 to 50 years inclusive
2. Non-smoker or light smoker of not more than 5 cigarettes a day. No smoking (or use of smoking substitute e.g. nicotine patch) is permitted from screening throughout the study
3. Body Mass Index (BMI) between 18 and 30.1 kg/m2 inclusive at screening
4. Considered as healthy after a comprehensive clinical assessment (detailed medical history and complete physical and neurological examination)
5. Normal Blood Pressure (BP) and Heart Rate (HR) at the screening visit after 10 minutes in supine position:

5.1. 95 mmHg ≤ Systolic Blood Pressure (SBP) ≤ 140 mmHg
5.2. 50 mmHg ≤ Diastolic Blood Pressure (DBP) ≤ 90 mmHg
5.3. 45 bpm ≤ HR ≤ 90 bpm
5.4. Or considered NCS by investigators
6. Normal ECG recording on a 12-lead ECG at the screening visit:
6.1. 120 ms < PR < 210 ms
6.2. QRS < 120 ms
6.3. QTcf ≤ 430 ms for male
6.4. No sign of any relevant trouble of sinusal automatism
6.5. Or considered as non-clinically significant by investigators
7. Laboratory parameters within the normal range of the laboratory (hematological, hormonology, blood chemistry tests, urinalysis). Individual values out of the normal range can be accepted if judged non-clinically significant by the Investigator; for example, isolated elevated bilirubin is acceptable if judged by the physician without clinical relevance (i.e. Gilbert's syndrome)
8. ALAT, ASAT and Creatinine values strictly within the normal range
9. A negative result for diagnostic test of SARS-CoV-2 at D-1
10. Normal dietary habits
11. Provision of written informed consent to participate as shown by a signature on the volunteer consent form, after reading the information and consent form, and after having the opportunity to discuss the trial with the investigator or his delegate
12. Able to communicate well with the Investigator and research staff and to comply with the requirements of the entire study
13. Covered by Health Insurance System and/or in compliance with the recommendations of National Law in force relating to biomedical research
14. Must agree to adhere to the contraception requirements defined in Section 4.3: use of condom by the male volunteer plus an effective method of contraception for the volunteer or their partner of childbearing potential from study drug administration until 90 days post-dosing OR use of a condom for 10 days post-dosing if the partner is known to be pregnant

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Male

Total final enrolment
64

Key exclusion criteria
1. Having previously received DNDI6148, or who participated in another clinical trial within 3 months prior and during the study, or 5times the halflife of the drug tested in the previous

clinical trial, whichever is longer (time calculated relative to the last dose in the previous clinical trial)
2. Any history (direct questioning) or presence (physical examination) of cardiovascular, pulmonary, gastrointestinal, hepatic, renal, metabolic, hematological, neurologic, psychiatric, systemic or infectious acute or chronic disease; including known or suspected HIV, HBV or HCV infection
3. With any clinically significant abnormality following review of prestudy laboratory tests, vital signs, full physical examination and ECG
4. Symptomatic hypotension whatever the decrease of blood pressure or asymptomatic postural hypotension defined by a decrease in SBP or DBP equal to or greater than 20 mmHg within two minutes when changing from the supine to the standing position
5. Who have a history of allergy, intolerance or photosensitivity to any drug
6. Who have a history of serious allergy, asthma, allergic skin rash or sensitivity to any drug
7. Who have a history of additional risk factors for "Torsades de Pointe" (e.g., heart failure, hypokalemia, family history of Long QT Syndrome)
8. Current suicide risk or history of suicide risk (CSSRS baseline: "yes" answer to items 4 and/or 5); participants with a "yes" answer for current suicide risk should be referred for psychiatric evaluation
9. Participants with rare hereditary problems of fructose intolerance, glucosegalactose malabsorption or sucraseisomaltase insufficiency
10. Who used a prescription medicine during the 28 days before the first dose of trial medication or use of an overthecounter medicine (including antacid drug, with the exception of acetaminophen (paracetamol)), during the 7 days before the first dose of trial medication
11. History or presence of drug or alcohol abuse (more than 14 units of alcohol per week, one unit = 8 g or about 10 mL of pure alcohol)
12. Excessive consumption of beverages with xanthine bases (more than one liter/day)
13. Who drink more than 8 cups daily of beverage containing caffeine
14. Who has regular daily consumption of more than 5 cigarettes daily, or use more than 3 grams (1/8 ounce) of tobacco
15. Who use dietary supplements or herbal remedies (such as St John's Wort) known to interfere with the CYP3A4 and/or Pgp metabolic pathways during the 28 days before the first dose of trial medication
16. Grapefruit should also be avoided during the 7 days before the first dose of trial medication
17. Positive Hepatitis B surface (HBs) antigen or anti Hepatitis C Virus (HCV) antibody, or positive results for Human Immunodeficiency Virus (HIV 1 or 2) tests
18. Positive results of screening for drugs of abuse (opiates, cocaine, amphetamine, cannabis, benzodiazepines)
19. Blood donation (including in the frame of a clinical trial) within 12 weeks before administration
20. General anaesthesia within 3 months before trial medication administration
21. Inability to abstain from intensive muscular effort
22. Who have any clinical condition or prior therapy which, in the opinion, of the Investigator, made the participant unsuitable for the study
23. Who had surgery (e.g. stomach bypass) or medical condition that might affect absorption of study drug taken orally
24. Who had febrile illness within 1 week before the start of the study
25. Participant who, in the judgment of the Investigator, is likely to be non-compliant or uncooperative during the study, or unable to cooperate because of a language problem, poor mental development
26. No possibility of contact in case of emergency
27. Exclusion period of a previous study
28. Administrative or legal supervision

29. Who are unwilling to give their informed consent
30. Participant who would receive more than 4500 euros as indemnities for his participation in biomedical research within the 12 last months, including the indemnities for the present study

Date of first enrolment
04/02/2020

Date of final enrolment
08/03/2022

Locations

Countries of recruitment
France

Study participating centre
Eurofins Optimed
1, rue des Essarts
Gières
France
38610

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)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Other unpublished results	version 1.0	08/06/2023	27/06/2023	No	No
Protocol file	version v7.0	17/06/2020	26/11/2020	No	No
Protocol file	version 8.0	19/11/2020	23/08/2022	No	No
Protocol file	version 9.0	24/02/2021	23/08/2022	No	No
Protocol file	version 10.0	21/09/2021	23/08/2022	No	No
Protocol file	version 11.0	25/11/2021	23/08/2022	No	No
Statistical Analysis Plan	version 2.0	04/04/2022	15/12/2022	No	No