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A study to assess the safety, drug levels in blood and markers of immune system response in patients after multiple doses of a new compound developed for the treatment of cutaneous leishmaniasis, CpG-ODN-D35

Submission date
30/11/2022

Registration date
05/12/2022

Last Edited
14/02/2023

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Leishmaniasis is an infectious disease caused by leishmania parasites and transmitted through the bite of a tiny mosquito. This mosquito lives in certain areas of Colombia, other countries in Latin America and many other countries in the world. Most of the time, the disease will present as ulcers in the skin.

There are only a few treatments available for this disease, including injections of meglumine antimoniate and pills of miltefosine, both have many adverse effects and do not have a good cure rate. The World Health Organization (WHO) encourages doctors to look for treatments that are more efficacious, and safer to use.

This study will allow assessing if it is safe for patients with cutaneous leishmaniasis (CL) to receive a new drug, named CpG ODN D35, alone and in combination with the existing oral treatment for the disease, miltefosine. It will also allow assessing the amount of CpG ODN D35 that gets into the blood, how this evolves with time and whether there are differences in the amounts in the blood between different dose strengths

Who can participate in the study?
Patients suffering from CL in its uncomplicated form

What does the study involve?
The research study participants will be split into groups and will be allocated to different groups of treatment, by a process called randomisation which is similar to a lottery.

The three different treatment options are:
1. CpG ODN D35

2. Miltefosine
3. CpG ODN D35 + miltefosine

CpG ODN D35 is specifically being developed for the treatment of CL. This drug can stimulate /enhance the immune system which can then better recognise and destroy the leishmania parasite. This should help stop the spread of the infection.

Participants assigned to receive CpG ODN D35 will receive one dose every two weeks, up to 3 doses in total, which will be injected in different locations in the fatty tissue around the belly button.

Miltefosine is one of the standard of care treatments for patients with CL in Colombia. Participants assigned to receive miltefosine will receive 1 pill of 50mg, three times per day for 28 days, to be swallowed with a glass of water, after a meal.

What are the possible benefits and risks of participating?
Miltefosine is one of the standard treatments for CL, therefore participants receiving this treatment can expect a cure at the end of the trial. The effects of treatment by CPG ODN D35 in humans are unknown at this stage of drug development, as only data on efficacy in animal models are available. Common side effects reported in people having received one dose of CPG ODN D35 were injection site reaction, nausea, fatigue, fever, muscle pain, and headache.

Common side effects reported with the use of miltefosine are nausea, vomiting, diarrhoea, abdominal pain, headache, loss of appetite, dizziness, pruritus, somnolence, changes in blood parameters monitoring how liver and kidneys are functioning, and fever. Less frequently we can observe lymph node size increase, fatigue, weakness, malaise, and motion sickness. Occasional nausea and vomiting may frequently be experienced.

Most of these events are mild and transient effects but there are other which, even if they haven’ t been reported, or reported infrequently, might be potentially severe. These are described below:

One potential side effect of CPG ODN D35 is cytokine release syndrome (CRS) which is an abnormal reaction of the immune system causing high fever, and multiple organ dysfunction that requires immediate care. It can be serious and result in death. This was not observed in previous study with CPG ODN D35, but it remains a potential risk.

As for any drug, there is a risk of allergy to CPG ODN D35. Allergy can give some papules, itching, and in the worst case, cause difficulty in breathing and low blood pressure requiring immediate intervention. Some severe skin allergic reactions were also reported for miltefosine on rare occasions.

The amounts of some cells from the blood may change after the injection of CPG ODN D35. If some cells decrease too much, there is an increased risk of infection or risk of bleeding.

As CPG ODN D35 is changing the immune system (which fights against infections), there could be a risk to take other drugs that also change this system. Therefore, it is not recommended to take other drugs while receiving CPG ODN D35 treatment without medical advice.

It is known from animal studies that miltefosine can cause malformations in the newborn and can also cause foetal death, therefore effective contraception is mandatory for women to be allowed to participate in the study.

There have been cases where the administration of miltefosine may have caused alterations to sexual function in men including a decrease of semen volume, dry ejaculation and scrotal tenderness. These effects do not occur very frequently and are transient as they disappear at the end of treatment. Recently, it has been observed that taking miltefosine may impair male fertility for an unknown period of time.

Miltefosine has recently been suspected to cause some eye complications such as keratitis, a disease of the eye, usually after a long treatment duration of more than 28 days. It can affect vision and lead to blindness if not treated.

Where is the study run from?
Program for the Study and Control of Tropical Diseases (PECET) (Colombia)

When is the study starting and how long is it expected to run for?
April 2022 to June 2024

Who is funding the study?
1. Drugs for Neglected Diseases initiative (DNDi, Switzerland)
2. Global Health Innovative Technology Fund (GHIT, Japan)

Who is the main contact?
Séverine Blesson (DNDi), sblesson@dndi.org (Switzerland)

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
PH22035

Study information

Scientific Title
A phase Ib, open-label, randomised, single-centre, multiple-dose-escalation study of the safety, tolerability, pharmacokinetics and pharmacodynamics of CpG ODN D35 after subcutaneous administration in participants with cutaneous leishmaniasis

Acronym
DNDi-CpG-02

Study objectives
The use of CpG ODN D35 in patients with uncomplicated cutaneous leishmaniasis alone and in combination with a standard therapeutic regimen is safe and will help to control the disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 25/11/2022, Comité de Ética Clinisalud del Sur S.A.S. (Carrera 48 N°46 A sur-107 oficina 1121, de la ciudad de Envigado, Colombia; +57 305 226 63 86; comite.etica@clinisaluddelsur.com), ref: CEI-0444-11-2022

Study design
Single-centre randomized interventional non-blinded with dose-escalation study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Cutaneous leishmaniasis

Interventions
The study is a phase Ib, single-centre, randomised, open-label study, evaluating multiple ascending doses of CpG ODN D35 administered subcutaneously in male and female participants aged between 18 and 50 years old with uncomplicated cutaneous leishmaniasis.
The study will consist of up to 4 cohorts. Participants in each cohort will receive multiple subcutaneous (SC) doses of CpG ODN D35 in a sequential escalating manner combined or not with miltefosine or miltefosine monotherapy (control arm).
There will be three arms distributed across the cohorts:
1. SC injection CpG ODN D35 on days 1, and 29
2. Multiple oral miltefosine 50 mg three times daily (tid) for 28 days
3. SC injection CpG ODN D35 on days 1, 15 and 29 + multiple oral miltefosine 50 mg tid for 28 days orally
Doses of CpG ODN D35 will be defined based on emerging data and will be named “Dose 1”,

“Dose 2” and “Dose 3” for the description below. Starting dose (Dose 1) will be 7.5 mg per dosing day.
Before exploring the combination arm (CpG ODN D35 + miltefosine) at a given dose, the trial design allows the SRC to review the data of the monotherapy arm CpG ODN D35 at the same dose. Therefore, the number of participants per cohort will be different in first and last cohort compared to others.
Within Cohort 1, 8 participants will be randomly assigned to CpG ODN D35 Dose 1 (6 participants) or miltefosine (2 participants). Within Cohort 2, 11 participants will be randomly assigned to CpG ODN D35 Dose 2 (6 participants) or miltefosine (2 participants) or the combination of CpG ODN D35 Dose 1 and miltefosine (3 participants). Within Cohort 3, 11 participants will be randomly assigned to CpG ODN D35 Dose 3 (6 participants) or miltefosine (2 participants) or the combination of CpG ODN D35 Dose 2 and miltefosine (3 participants). Within Cohort 4, 5 participants will be randomly assigned to miltefosine (2 participants) or the combination of CpG ODN D35 Dose 3 and miltefosine (3 participants).

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
CpG ODN D35, miltefosine

Primary outcome(s)
Incidence of treatment-emergent adverse events recorded from the first dose up to day 90, assessed as the proportion of participants with treatment-emergent adverse events in each treatment group

Key secondary outcome(s))
The following PK parameters will be derived from plasma CpG ODN D35 concentrations in samples
1. Geometric mean (GM) of CpG ODN D35 maximum concentration (Cmax) on days 1, 14 and 29
2. Median time of maximum concentration (tmax) on days 1, 14 and 29
3. Geometric mean (GM) of CpG ODN D35 Area Under the Curve from 0 to t (AUC0-t) on days 1, 14 and 29

Completion date
30/06/2024

Eligibility

Key inclusion criteria
1. Male or female participants aged between 18 to 50 years old at the time of obtaining the informed consent.
2. Body weight ≥55 kg to ≤ 90 kg, body mass index (BMI) 18 to 30.1 kg/m2. BMI = body weight (kg) / [height (m)]2
3. Provision of written informed consent to participate as shown by a signature on the participant information sheet and consent form, after reading the information sheet and consent form, and after having the opportunity to discuss the trial with the Investigator or his /her delegate.

4. Confirmed diagnosis of cutaneous leishmaniasis by at least one of the following methods conducted as per standard of care at the clinical centre within 56 days before the first dose administration of the IMP:
4.1. Microscopic identification of amastigotes in stained lesion tissue, or
4.2. Demonstration of leishmania by polymerase chain reaction (PCR), or
4.3. Positive culture for promastigotes.
5. CL lesions that satisfy the following criteria:
5.1. Number of lesions: ≤ 4,
5.2. Lesion size: ≤ 4 cm (longest diameter), and
5.3. No mucosal involvement.
6. Normal blood pressure (BP): systolic blood pressure (SBP) between ≥100 and ≤140 mmHg, diastolic blood pressure (DBP) ≤ 90 mmHg, measured after 10 min rest in a supine position, within 28 days before the first dose administration of the IMP.
7. A resting heart rate (HR) between ≥45 and ≤90 bpm measured after 10 min rest in a supine position, within 28 days before the first dose administration of the IMP.
8. ECG recording after 10 min rest in a supine position without clinically significant abnormality, including a Fridericia's corrected interval between Q and T waves (QTcF) measure of ≤ 450 msec, within 28 days before the first dose administration of the IMP.
9. No clinically significant history of previous allergy/sensitivity to CpG ODN D35 or any of the excipients contained within the IMP(s).
10. 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.
11. Participants with a negative urinary drug of abuse (DoA) screen (including alcohol) test results, determined within 28 days before the first dose administration of the IMP (N.B.: A positive test result may be repeated once at the Investigator's discretion).
12. Participants must be available to complete the study (including all follow-up visits).
13. Participants must satisfy an Investigator about their fitness to participate in the study.
14. Participants registered with the Colombian Health Insurance System.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
50 years

Sex
All

Key exclusion criteria
1. Female with a positive highly sensitive blood or urine pregnancy test at screening/admission or who is breastfeeding, or lactating
2. Female of childbearing potential who does not agree to follow the contraception

requirements defined in the protocol
3. Within 8 weeks (56 days) of having received treatment for leishmaniasis (topical or systemic) with any method, which likely in the opinion of the Principal Investigator (PI) could modify the course of the leishmania infection
4. Behavioural, cognitive, or psychiatric disease that in the opinion of the Investigator affects the ability of the participant to understand and cooperate with the study protocol
5. 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
6. Individual or family history of pre-existing autoimmune or antibody-mediated diseases including (but not limited to): systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, type 1 diabetes mellitus, auto-immune thyroiditis, Basedow syndrome, autoimmune thrombocytopenia; or proteinuria (greater than trace protein on urine dipstick testing)
7. History of allergy, hay fever, intolerance or photosensitivity to any drug or have a history of serious allergy, asthma, allergic skin rash or sensitivity to any drug
8. Participants who are taking, or have taken, any prescribed or over-the-counter (OTC) drug (including non-steroidal anti-inflammatory drugs (NSAID)) in the 28 days or 5 half-lives (whichever is longer) before IMP administration. Administration of up to 3 g of paracetamol per day within 7 days of IMP administration is allowed if not used to treat fever
9. Participants who have received any prophylactic vaccine (including COVID-19 vaccine) or immunization within the last 28 days or use of corticosteroids or immunosuppressive drugs within 28 days of IMP administration.
10. Participants with febrile illness or infectious illness within 2 weeks of IMP administration
11. Participants with positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) and or human immunodeficiency virus (HIV) tests results at screening
12. Positive antigenic COVID-19 test at admission
13. Donation or loss of greater than 500 mL of blood within the previous 3 months prior to IMP administration.
14. Major surgery within 12 weeks prior to screening.
15. Participants who are known or suspected alcohol users above 14 units of alcohol per week, one unit = 8 g or about 10 mL of pure alcohol. Positive alcohol test at screening or admission.
16. Participants who smoke more than 5 cigarettes per day on average or consume an equivalent nicotine quantity through nicotine-containing products (including e-cigarettes, nicotine patches or gums).
17. Participants unable to abstain from smoking without replacement by nicotine products during the hospitalisation periods.
18. Demonstrating excess in caffeine/xanthine consumption (more than 6 cups of coffee or equivalent a day).
19. History of use of drugs of abuse in the past 2 years.
20. Participants who do not have suitable veins for multiple venepunctures/cannulations.
21. Participants who have any clinical condition or prior therapy which, in the opinion of the Investigator, could jeopardize the safety or rights of a participant participating in the trial or would render them unable to comply with the protocol.
22. Participation in a non-marketed drug clinical study within 3 months or five half-lives (whichever is longer) or a marketed drug clinical study within 30 days or five half-lives (whichever is longer) before the first dose of IMP (washout period between studies is defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study).
23. Participants who are study site employees, or immediate family members of a study site or Sponsor employee.

24. Inability to communicate well with the Investigators (e.g., language problem, poor mental development, or impaired cerebral function).
25. Hypersensitivity to miltefosine or to any study medication excipients

Date of first enrolment
01/03/2023

Date of final enrolment
31/12/2023

Locations

Countries of recruitment
Colombia

Study participating centre
Program for the Study and Control of Tropical Diseases (PECET)
Clinical Trial Unit
Programa de Estudio y Control de Enfermedades Tropicales - PECET
School of Medicine, University of Antioquia,
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Sponsor information

Organisation
Drugs for Neglected Diseases Initiative

ROR
https://ror.org/022mz6y25

Funder(s)

Funder type
Charity

Funder Name
Global Health Innovative Technology Fund

Alternative Name(s)

GHIT Fund, , Japanese Global Health Innovative Technology Fund, The Global Health Innovative Technology Fund, GHIT

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Japan

Funder Name
Drugs for Neglected Diseases initiative

Alternative Name(s)
DNDi

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available later

IPD sharing plan summary
Data sharing statement to be made available at a later date