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A study to assess safety, drug levels in blood and markers of immune system response after an escalating single dose of a new compound developed for the treatment of cutaneous leishmaniasis, CpG-ODN-D35, in healthy male subjects

Submission date
29/06/2021

Recruitment status
No longer recruiting

Registration date
12/07/2021

Overall study status
Completed

Last Edited
12/05/2023

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
The study sponsor (the Drugs for Neglected Diseases initiative (DNDi)) is developing CpG ODN D35 for the treatment of a disease called cutaneous leishmaniasis (CL). This disease is caused by a parasite that 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 that are less developed with high rates of poverty, malnutrition and poor housing conditions. There are three main forms of the disease that 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 which can cause disfiguration and deformities in physical appearance leading to severe social stigma.
This study will be the first study in which CpG ODN D35 has been tested in humans. The main objectives of this study are as follows:
1. To determine the safety and tolerability (degree to which side effects of a drug can be tolerated) of CpG ODN D35 when it is administered as a subcutaneous injection (injection into the tissue layer between the skin and muscle) at different dose strengths on one occasion.
2. To investigate the concentration of CpG ODN D35 in the blood, how this changes over a period of time and whether there are differences in the concentration profile between different dose strengths.

Who can participate?
Healthy males between 18 and 50 years of age

What does the study involve?
Participants will be split into four groups of eight, each evaluating a different dose of CpG ODN

D35. Participants will either be given CpG ODN D35 or a placebo (which contains no active drug). Both CpG ODN D35 and the placebo will be injected in the form of one or more subcutaneous injections (injection into the fatty tissue layer between the skin and muscle). Follow-up will be organised over a period of 14 days after dosing.

What are the possible benefits and risks of participating?
Taking part in this study is not expected to provide the participant with any direct medical benefit. However, the information from this study may help to improve the treatment of cutaneous leishmaniasis. This is the first study to test CpG ODN D35 in humans and therefore the researchers have limited information on what the potential side effects of CpG ODN D35 could be in humans. Potential side effects are described in the Informed Consent document provided. The most likely events that may be observed are pain, swelling and hardness of the skin around the injection site, and flu-like symptoms (i.e., chills, headache, fatigue and elevated body temperature).

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

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

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

Who is the main contact?
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Contact information

Type(s)
Public

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Clinical Trials Information System (CTIS)
2021-001179-18

Integrated Research Application System (IRAS)
297265

Protocol serial number
DNDiCpG01, RD 777/35000

Study information

Scientific Title
A Phase I, double-blind, randomised, single-centre, parallel-group, single ascending dose, placebo-controlled study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of CpG ODN D35 after subcutaneous administration in healthy male subjects

Study objectives
The primary objective of this study is to assess the safety and tolerability of a single subcutaneous dose of CpG ODN D35 in healthy male subjects.

The secondary objective of this study is to determine pharmacokinetic (PK) parameters of CpG ODN D35 in plasma after a single subcutaneous dose in healthy male subjects.

Study hypothesis:
CpG ODN D35 will be well tolerated in healthy volunteers to allow in the future to be tested as a potential adjuvant drug for the treatment of patients suffering from complicated cutaneous leishmaniasis disease or patients with leishmaniasis recidivans.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 14/05/2021, Wales Research Ethics Committee 1 - Cardiff (Health and Care Research Wales, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; +44 (0)7920565664, +44 (0)2920230457, +44 (0)7787371748; Wales.REC1@wales.nhs.uk), REC ref: 21/WA/0094

Study design
Phase I single-centre double-blind randomized placebo-controlled parallel-group single ascending dose study

Primary study design
Interventional

Study type(s)
Safety

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

Interventions

Participants will be split into four groups of eight to receive a single subcutaneous (SC) dose of CpG ODN D35 (six subjects) or placebo (two subjects). Each group evaluates a different dose strength of CpG ODN D35 starting at 7.5 mg in a 0.5 ml injection in Group 1 and increasing up to a maximum of 180 mg (12 ml as six injections) in Group 4. Laboratory, clinical and ECG follow-up will be organised over a period of 14 days after dosing.

Intervention Type
Drug

Phase
Phase I

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

Primary outcome(s)
Safety and tolerability of CpG ODN D35 after a single dose 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 (13 to 14 days post 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 (13 to 14 days post dose)
3. Causality of AEs, based on the clinical judgement of the investigator, occurring from first dosing up to post-study follow-up visit (13 to 14 days post dose). The possible relationship between the AE and the study drug will be quoted as follows:
3.1. Definitely related. The AE and administration of the study agent are related in time, and a direct association can be demonstrated.
3.2. Probably related. The AE and administration of the study agent are reasonably related in time, and the AE is more likely explained by the study agent than other causes.
3.3. Possibly related. The AE and administration of the study agent are reasonably related in time, and the AE can be explained equally well by causes other than the study agent.
3.4. Probably not related. A potential relationship between the study agent and the AE could exist (i.e., the possibility cannot be excluded), but the AE is most likely explained by causes other than the study agent.
3.5. Not related. The AE is clearly explained by another cause not related to the study agent.
4. Severity of AEs assessed based on the clinical judgement of the investigator, occurring from first dosing up to post-study follow-up visit (13 to 14 days post dose). The severity of the AEs will be determined using the following grading scale: Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. U.S. Department of Health and Human Services Food and Drug Administration Centre for Biologics Evaluation and Research. September 2007.

Key secondary outcome(s))
The following PK parameters will be derived from plasma CpG ODN D35 concentrations (additional parameters may
be derived, if applicable) in samples taken at the following timepoints: Day 1: pre-dose, 10 min, 20 min, 30 min, 45 min, 1 h, 2 h & 4 hr post-dose:
1. Cmax (ng/ml): observed maximum plasma concentration
2. Tmax (h): first time to reach Cmax
3. λz (1/h): apparent first-order terminal elimination rate constant
4. t1/2 (h): plasma elimination half-life
5. AUClast (ng.h/ml): AUC from 0 to the time of the last quantifiable concentration

6. AUCall (ng.h/ml): AUC from 0 to the time of the last observation, regardless of whether the last concentration is measurable or not
7. AUC0-24 (ng.h/ml): AUC over 24 hours
8. AUC0-inf (ng.h/ml): AUC extrapolated to infinity
9. AUC% extrapolated (%): residual area

Completion date
13/10/2021

Eligibility

Key inclusion criteria
1. Male healthy subjects 18 to 50 years old at the time of obtaining the informed consent
2. Body weight ≥60 kg to ≤90 kg, 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. Normal blood pressure: systolic blood pressure between ≥100 and ≤140 mmHg, diastolic blood pressure ≤90 mmHg, measured after 10 min rest in a supine position at Screening, admission, and pre-dose
5. A resting heart rate (HR) between ≥45 and ≤90 bpm measured after 10 min rest in a supine position at Screening, admission, and pre-dose
6. ECG recording without clinically significant abnormality, including a QTcF measure of ≤450 msec
7. Male participant (and partner of childbearing potential) willing to use a highly effective method of contraception, if applicable (unless anatomically sterile or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the participant) from first dose until 3 months after the last dose of IMP
8. No clinically significant history of previous allergy/sensitivity to CpG ODN D35 or any of the excipients contained within the IMP(s)
9. 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
10. Participant with a negative urinary drugs of abuse (DOA) screen (including alcohol/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)
11. Participant must be available to complete the study (including all follow-up visits)
12. Participant must satisfy an Investigator about his fitness to participate in the study

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
50 years

Sex
Male

Total final enrolment
54

Key exclusion criteria
1. 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
2. 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
3. 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)
4. 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
5. Subjects who are taking, or have taken, any prescribed or over-the-counter 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
6. Subjects 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
7. Subjects with febrile illness or infectious illness within 2 weeks of IMP administration
8. Subjects with positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) and or human immunodeficiency virus (HIV) tests results at Screening
9. Positive RT-PCR COVID-19 test at admission
10. Donation or loss of greater than 500 ml of blood within the previous 3 months prior to IMP administration
11. Major surgery within 12 weeks prior to Screening
12. Subjects who are known or suspected alcohol abusers (more than 14 units of alcohol per week, one unit = 8 g or about 10 ml of pure alcohol). Positive alcohol test at Screening or admission
13. Demonstrating excess caffeine/xanthine consumption (more than 6 cups of coffee or equivalent a day)
14. History of use of drugs of abuse in the past 2 years
15. Subjects who do not have suitable veins for multiple venepunctures/cannulation
16. Subjects who have any clinical condition or prior therapy which, in the opinion of the Investigator, could jeopardize the safety or rights of a volunteer participating in the trial or would render them unable to comply with the protocol
17. 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)
18. Subjects who are study site employees, or immediate family members of a study site or sponsor employee
19. Inability to communicate well with the Investigators (i.e., language problem, poor mental development or impaired cerebral function)
20. Users of nicotine products i.e., current smokers or ex-smokers who have smoked within the 6 months prior to Screening or users of cigarette replacements (i.e., e-cigarettes, nicotine patches or gums)

Date of first enrolment
01/06/2021

Date of final enrolment
01/10/2021

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre
Simbec-Orion Clinical Pharmacology
Merthyr Tydfil Industrial Park
Cardiff Road
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CF48 4DR

Sponsor information

Organisation
Drugs for Neglected Diseases Initiative

ROR
https://ror.org/022mz6y25

Funder(s)

Funder type
Industry

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 underlying the results of this study are available upon request because they contain potentially sensitive information. Interested researchers may contact the Drugs for Neglected Diseases initiative (DNDi), commissioner of this study, for data access requests via email at CTdata@dndi.org. Researchers may also request data by completing the form available at https://www.dndi.org/category/clinical-trials/. In this, they confirm that they will share data and results with DNDi and will publish any results open access.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Basic results			12/05/2023	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	version 2.0	12/05/2021	04/08/2021	No	Yes
Protocol file	version 4.0	23/06/2021	04/08/2021	No	No