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Chagas disease drug development

Submission date 11/06/2021	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 01/07/2021	**Overall study status** Ongoing	
Last Edited 10/09/2025	**Condition category** Infections and Infestations	

Plain English summary of protocol

Background and study aims
Chagas disease is caused by a parasite named Trypanosoma cruzi and vector transmitted by an insect known as “kissing bug”. The lack of a comprehensive understanding of this disease has slowed the discovery of new treatments. It is generally agreed that new, safe, effective, and reasonably priced drugs to treat Chagas disease are needed.

It is currently very difficult to define whether a new drug is effective to treat Chagas. A significant drop in the antibody level and absence of detectable parasites in the blood are considered currently by regulatory authorities, such as the US FDA, as the most important determinants of treatment response. Unfortunately, as this significant drop in antibodies can take too long to happen, is not quick enough to select drugs when these have recently been developed. We designed this study to analyse the parasite changing aspects and how these relate to treatment drugs because we think that this information might help to select new treatments more precisely.

Who can participate?
Adult patients with chronic Chagas disease.

What does the study involve?
Patients invited to take part in the study will be informed about the study and receive an electrocardiogram (ECG) to measure the electrical activity of the heart and a blood sample extraction to measure how many parasites there are in the blood. Female patients of childbearing potential will receive a pregnancy test. If the amount of parasites circulating in the blood at initial assessment are enough to be studied and participants are happy to continue to take part in the trial they will be given the next appointment date.

At the next appointment, participants will be either followed up by a study nurse at your domicile or seen at the outpatient clinic. The visits will be bi-weekly during the first month and there will be blood extractions at each visit to determine how the parasites circulate, prior to receiving treatment. At the end of the first month, participants will be randomly assigned (like the toss of a coin) to receive one of three treatments: Benznidazole or Nifurtimox or Posaconazole. On the day of receiving the dose of treatment, blood will be extracted 4 times. The following 6 days after treatment, participants will be seen daily and one blood sample will be taken per day. From 7 days after treatment, a blood sample will be extracted every other day

the following week and then once a week until the end of the study. During the study participation, participants are reminded not to take herbal medicines, food supplements, and energy drinks for a period of 4 months after initiation of treatment.

Each visit should take approximately 20 min and the total time required to participate in the study is approximately 4 months. After finishing participation in the trial, participants will receive a full course of treatment as per national guidelines.

What are the possible benefits and risks of participating?
There will be no direct or personal benefit to the subjects taking part in this research. However, there is the chance of contributing to science. Patients may have the satisfaction of contributing to clinical research that can help to the advancement of therapy, improving the lives of other future patients affected by the same disease. Moreover, for the simple fact that subjects are taking part in a clinical trial, they will be monitored more frequently and in greater detail than usual.

Patients may experience mild discomfort when a blood sample is taken and it is also possible (although not likely) that a bruise is formed. The research doctor and staff will do their best to minimize any possible discomfort or harm to the patients involved. The total volume of blood collected during the 3 months of the trial is about 460 ml.

All drugs used in the study (benznidazole, nifurtimox, and posaconazole), are well-known drugs and their most common reactions include hypersensitivity (mainly in the form of a rash is seen in 29–50% of patients), digestive intolerance (seen in 5–15% of patients), and general symptoms (seen in 40% of patients) such as loss of appetite, weakness/lack of energy, headache, and sleep disorders. Bone marrow neuropathy and depression are considered rare side effects. Treatment is interrupted in 9–29% of cases, although these reactions are reversible and severity only occurs in less than 1% of cases. Anyway, because patients will be given a much lower than normal dosage, they would not be expected to have any adverse reactions. In any case, participants are encouraged to tell the medical researchers anything that might bother them during the study. On the other hand, the medical researcher can interrupt the participation in the study of any subject if it is deemed necessary.

Where is the study run from?
Oswaldo Cruz Foundation-Fiocruz Minas Gerais (Brazil)

When is the study starting and how long is it expected to run for?
From June 2020 to June 2027

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
PAR21001, Wellcome Trust grant 222754/Z/21/Z

Study information

Scientific Title
Pilot Phase II trial to optimise pharmacometric assessments in Chagas disease

Acronym
CHARM

Study objectives
The parasitemia fluctuates within a steady state equilibrium in chronic Chagas disease.
The rate of decline of the qPCR is a useful pharmacometric measure for Chagas treatment efficacy

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 10/08/2021, Oxford Tropical Research Ethics Committee (Research Services, University Offices Wellington Square, Oxford, OX1 2JD, United Kingdom; +44 (0)1865 (2)82106; oxtrec@admin.ox.ac.uk), ref: 16-21
2. Approved 07/09/2023, Comitê de Ética do IRR/FIOCRUZ Minas (Avenida Augusto de Lima, 1715, Belo Horizonte , 30.190-009, Brazil; +55 (0)31 3349 7825; cepcoord.minas@fiocruz.br), ref: Número do Parecer: 6.160.759
3. Approved 12/02/2024, Comissão Nacional de Ética em Pesquisa (SRTV 701, Via W 5 Norte, lote D - Edifício PO 700, 3º andar – Asa Norte, Brasilia, DF, 70719-040, Brazil; +55 (0)61 3315 5878; conep@saude.gov.br), ref: N/A

Primary study design
Interventional

Study design

Descriptive study of within-host parasite dynamics followed by a three-arm randomized trial of pharmacokinetic-pharmacodynamic properties of sub-curative drug doses

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Chronic Chagas disease

Interventions
In the first stage, baseline parasitaemia will be quantitated twice weekly over the course of one month to characterize the natural variation in T. cruzi blood stage densities for individuals at a quasi steady-state.

The second stage will consist of a randomised assignment to a sub-curative regimen followed by intensive pharmacokinetic and pharmacodynamic sampling to characterize drug exposure-parasite density relationships very precisely.

The third stage will consist of weekly blood measurements of parasite density to monitor and quantify recrudescent parasitaemia and the new steady state density following the sub-curative regimen. After this the volunteer will receive definitive treatment.

Participants eligible for stage 2 of the study will be randomised to a predicted sub-curative dose regimen of either benznidazole, nifurtimox or posaconazole. The randomisation will be in previously sealed envelopes. The exact dosing and number of doses will be adapted over the course of the study, but no single dose will be above the following thresholds defined for each drug:
1. Benznidazole: maximum tolerated daily dose is 10 mg/kg
2. Nifurtimox: maximum tolerated dose of 10 mg/kg
3. Posaconazole: maximum tolerated dose of 15 mg/kg

Sub-curative dosing: first 6 individuals:
The starting sub-curative regimens for the first 6 enrolled individuals who complete stage 2 of the study will be:
1. A single dose of benznidazole 100 mg
2. A single dose of nifurtimox 120 mg
3. A single dose of posaconazole 600 mg (a higher dose of posaconazole is necessary as it has weak anti-parasitic action, acting only on the tissue-stages).

Sub-curative dosing: subsequent individuals:
Subsequent individuals will be dosed according to a model-based approach that will use all previously accrued data. Full details of the model are given in the Statistical Analysis Plan – here we give a high-level overview of what the model-based adaptation is doing and what it is optimising.
For benznidazole and nifurtimox, we want to demonstrate, as proof-of-concept, that it is possible to target the in vivo ED95 of each drug (in the context of the study, the ED95 is defined as the mg/kg dose that results in a pharmacodynamic effect approximately equal to 95% of the maximum parasite clearance effect, when constrained to the range of tolerated doses; after completion of the study we will have drug measurement data and the ED95 will be defined as the blood concentration that results in a pharmacodynamic effect equal to 95% of the maximum parasite clearance effect). In addition, we want to determine the minimum duration of dosing at

the predicted ED95 that results in blood stage parasite clearance (i.e. parasite densities below the lower limit of detection) within one week for 90% of individuals (undetectable blood stage parasitaemia at or before day 7).

For posaconazole, we want to characterise blood stage parasite clearance for a drug that effects only the tissue stages (therefore blood clearance represents natural parasite clearance in absence of re-population from the tissue reservoir). We define the target regimen as the shortest regimen that results in full blood stage parasite clearance within one week for 90% of individuals (undetectable blood stage parasitaemia at or before day 7).

In order to assign dose regimens that meet both of these objectives (targeting the ED95 for benznidazole and nifurtimox; and targeting full parasite clearance within one week for benznidazole, nifurtimox, and posaconazole), we will fit a log-linear model to serial parasite density measurements from each participant, using all baseline data to estimate the baseline quasi steady-state. The output parasite clearance rate (expressed as a half-life in units of hours) will then be the main pharmacodynamic summary used to adapt the doses. To estimate the mg /kg dose approximating the ED95 we will fit a Bayesian EMAX model to the data with mg/kg dose of benznidazole/nifurtimox as the proxy for drug exposure (pharmacokinetic data will only be available at the end of the study). To estimate the minimum duration of dosing that results in parasite clearance by day 7 in 90% of participants, we will fit a logistic regression model with drug exposure characterised as predicted area under the concentration curve (AUC: this allows single dose regimens and multiple dose regimens to be modelled on the same scale) as the predictor variable and parasite clearance by day 7 (as a binary outcome) as the outcome variable.

After every batch of 6 individuals studied, we will re-calculate the predicted ED95 and the minimum duration of dosing to obtain parasite clearance by day 7 for each drug. These estimated doses and durations will then be administered to the next batch of 6 individuals.

Redosing after negligible parasite reduction:
It is possible that some of the doses trialled (most likely for the first batch of individuals- as there are limited data on single-dose responses) will be too low and will result in negligible parasite clearance in the first week. We define “negligible parasite reduction” as an estimated reduction of less than 50% from the baseline parasite density (as all participants should have baseline densities >2 parasites per ml, this implies a nadir >1 parasite per ml which remains above the lower limit of quantification). An individual whose parasite reduction is determined to be negligible will be re-dosed, using their observed data to update the dose-response model, with the updated estimate of the necessary dose/duration needed to clear parasites from the blood within 1 week (this implies that they will be re-dosed with a higher dose regimen). If dose increases are needed above the maximum tolerated individual dose then repeat daily dosing will be employed.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Benznidazole, nifurtimox, posaconazole

Primary outcome(s)

Stage 1: Wavelength and amplitude of the temporal fluctuations in the blood-stage parasite density estimated from twice weekly blood-stage parasite densities taken over one month
Stage 2: Parasite clearance half-life in blood using serial qPCR after sub-curative drug regimens
Stage 3: Assessment of tissue-stage load measured by time to recrudescent parasite density detectable by qPCR

Key secondary outcome(s)
1. Time to reach new steady-state parasite density measured using qPCR from the time of the dose with suboptimal treatment until up to 12 weeks
2. Fold-change in parasite density between estimated baseline steady-state and recrudescent steady state

Completion date
30/06/2027

Eligibility

Key inclusion criteria
1. Adult volunteers with chronic T. cruzi infection, a blood-stage parasite density of at least 2 parasite equivalents per mL, with or without end-organ involvement and:
1.1. Participant is willing and able to give informed consent for participation in the study.
1.2. Adult patients, male or female, aged over 18 years and less than 99 years.
1.3. Lives in the Belo Horizonte metropolitan area and can comply with study procedures.
1.4. Circulating parasitaemia greater or equal to 2 parasites equivalent per mL.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
99 Years

Sex
All

Key exclusion criteria
1. Has received prior treatment with benznidazole, nifurtimox or posaconazole (either completely or incompletely).
2. History of hypersensitivity, allergic, or serious adverse reactions to any nitroimidazole compound, posaconazole and/or its components.
3. Inability to attend follow-up visits on the stipulated dates.
4. Acute or chronic health problems that, in the opinion of the principal investigator, may

interfere with study completion.
5. Alcohol or drug dependence.
6. HIV infection or is immunocompromised.
7. Pregnant or breastfeeding.
8. Patients taking any immunosuppressant drugs.
9. QT prolongation (>450 ms for males; >470 ms for females).
10. Basic laboratory parameters outside the normal range or that are considered clinically relevant by the physician responsible for the patient.
10.1. Total white blood cell counts outside the normal range, as defined by an acceptable margin of +/- 5% (3,800 - 10,500 / mm3);
10.2. Transaminases (ALT and AST) outside the normal range, as defined by 25% above the upper limit of normal (ULN, > 1.25 x ULN).
11. Therapy with drugs metabolized by CYP3A4, such as terfenadine, astemizole, pimozide, halofantrine or quinidine, and HMG-CoA reductase inhibitors (simvastatin, lovastatin, and atorvastatin).
12. Patients receiving treatment with proton pump inhibitors or H2 receptor antagonists, phenytoin, efavirenz, and rifabutin, or who cannot discontinue it during the study period.
13. Patients receiving any drugs known to prolong the QT interval significantly.

Date of first enrolment
18/06/2024

Date of final enrolment
31/12/2026

Locations

Countries of recruitment
Brazil

Study participating centre
Oswaldo Cruz Foundation-Fiocruz Minas Gerais
Av. Augusto de Lima, 1715 - Barro Preto
Belo Horizonte - MG
Brazil
30190-002

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

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

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publically available repository. We are committed to open research and to ensuring full reproducibility of all results. The clinical trial data will be part of IDDO data platform (https://www.iddo.org/research-themes/chagas-disease). The intention is to facilitate meta-analysis of clinical trials in Chagas disease and to ensure data perpetuity. Data will be available via the IDDO data governance framework (managed data access via an independent committee). The Clinical trial data that will be in the platform is:
1. Serial qPCR data (the main pharmacodynamic variable of interest) will be made publicly available alongside code and software for the pharmacodynamic modeling on a github repository. Releases of this repository will archived on Zenodo.
2. Clinical trial data and meta-data will be shared with IDDO and available via their data governance structure

IPD sharing plan summary
Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v1.0	07/04/2021	08/07/2021	No	Yes