Informed Consent Form for Research Involving Human Subjects

Protocol Title:	New Chemotherapy Regimens and Biomarkers for Chagas Disease
Study Acronym/Nickname:	TESEO
ClinicalTrials.gov Identifier:	NCT03981523
Protocol Number/ Version/ Date:	743474-14 / Version *2.4 / May 13th, 2020*
Principal Investigators:	Dr. Faustino Torrico, M.D., Ph.D. Fundación Ciencia y Estudios Aplicados para el Desarrollo en Salud y Medio Ambiente (CEADES) Cochabamba, Bolivia Dr. Joaquim Gascón, M.D., Ph.D. Barcelona Institute for Global Health (ISGlobal) Barcelona, Spain Dr. Igor C. Almeida, D.Sc. University of Texas at El Paso El Paso, Texas, U.S.A.
Sponsor:	University of Texas at El Paso (UTEP) El Paso, Texas, USA

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

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INFORMATION ABOUT THE STUDY

Introduction

You have been diagnosed with Chagas disease. Maybe you *are* aware that this disease is common in Bolivia. There are three main ways of transmission of the parasite that causes Chagas disease: (1) through *the transmitting* insect (*kissing bug*), (2) through blood transfusion, and (3) mother to *the* newborn, either during pregnancy or childbirth. Chagas disease occurs in two phases: acute (when new infection occurs) and chronic (when the disease is already in the body for a long period). The latter can be divided into three forms: indeterminate or latent, cardiac and digestive. You are in the early indeterminate (asymptomatic) or cardiac phase, without major health problems, and can benefit from the treatment against Chagas disease. Please note, however, that even with treatment, it is possible that complications can arise later and in some rare cases, death can occur due to the disease.

The only drugs currently available for the treatment of Chagas disease are Benznidazole (BZN) and Nifurtimox (NFX). These drugs have been around for more than 40 years and their effectiveness is well documented, but they can cause adverse effects, especially when used in adults. Therefore, it is of interest to know if these drugs currently available for the treatment of Chagas disease (BZN and NFX) used at lower doses and a longer and/or shorter treatment time, may be equally or more effective and with fewer adverse effects than in the current form of actual treatment used.

The current tests being used to diagnose Chagas can take years to show a negative result even after a person has received treatment and the treatment has shown to be effective. This prevents that, during all those years after treatment, the affected person *knows* the definitive outcome of the treatment. This study will also use new diagnostic tests (biomarkers) to screen for Chagas disease and to see if in a few months, the results become negative. These tests can be a new and useful tool to help doctors and patients at an early stage of the disease to evaluate the result of the treatment.

Since you are a patient affected by Chagas disease, we invite you to participate in this study. Please take your time to making a decision and feel free to discuss it with your friends and family. Before agreeing to take part in this research study, it is important that you read the consent form that describes the study. Please ask the study researcher or the study staff to explain any words or information that you do not clearly understand.

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Duration and size of the study

A total of 450 patients in Bolivia will take part in this study. Your participation in the study will be approximately three years. This includes the initial screening period of 28 days, then the weekly treatment period of 30, 60 or 90 days and then follow-up visits in the months following the end of treatment (at 4, 6, 12, 18, 24, 30, and 36 months after the beginning of treatment).

Study Treatment

The study drugs are (BZN) benznidazole and nifurtimox (NFX), which have been used for years in the treatment of Chagas disease. BZN will be donated by ELEA Phoenix, Argentina. NFX will be donated by Bayer, El Salvador. Each of these medications will be administered in three different doses, in such a way that there will be a total of six treatment groups in the study, with 75 patients each.

Arm 1 (BZN-60): BZN at 150 mg, two times a day for 60 days (Standard of Care, SoC)
Arm 2 (BZN-30): BZN at 150 mg, once a day for 30 days
Arm 3 (BZN-90): BZN at 150 mg, once a day for 90 days
Arm 4 (NFX-60): NFX at 240 mg, two times a day for 60 days (SoC)
Arm 5 (NFX-30): NFX at 240 mg, two times a day for 30 days
Arm 6 (NFX- 90): NFX at 240 mg, once a day for 90 days

You will be assigned to one of these six treatment arms. You will know at all times which type of medication you are taking, the dose and the duration of the treatment. At the end of the study, information on the outcome of the treatment will be revealed. If your results indicated that the treatment was ineffective, you will be referred to receive the standard treatment for Chagas.

You will receive the assigned treatment during a period of 30, 60 or 90 days. The medication will be administered orally, and must be taken daily, according to the treatment.

Depending on your assigned treatment group, the **study medication must be taken daily by mouth, with food, as indicated in your "Treatment Study Journal"**. You will be asked to complete your treatment card information and fill in the "Problems" column if you have any difficulties related to the treatment. We must emphasize that **you cannot drink alcoholic drinks during the entire period of treatment**.

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Study Procedures

If you agree to participate in this study, in the first 28 days, there will be a screening process, where you will undergo a complete physical exam and have blood samples taken for a complete blood count, liver and kidney function tests and also an analysis to see if you have small trace (DNA) of the parasite in your blood. An electrocardiogram will also be completed. In addition, there will be a pregnancy test for women of childbearing age. A determination to participate in the study will be made after these procedures are completed and requirements are met. Blood sampling and electrocardiogram will be repeated on day 0. Additionaly, a urine sample will be collected during the study visits.

If you meet the study inclusion criteria and are still interested in participating, you will be assigned to one of 6 treatment groups on study day 1. You must then return to the clinic, weekly and/or biweekly until the end of the treatment, according to your treatment group, and for the follow-up visits (4, 6, 12,18, 24, 30, and 36 months), for a total of 14, 15 or 17 visits, according to your assigned treatment group.

A physical exam will be performed every two weeks, and blood and urine will be taken every week. Approximately 3-25 ml (25 ml is about two tablespoons) of blood will be drawn, depending on your assigned treatment group, to check for safety and efficacy of the treatment. Moreover, urine samples (approximately 10 ml) will be collected according to the treatment arm (30, 60, or 90 days). An electrocardiogram will also be performed before starting treatment and during the follow-up visits at the 12^{th}, 24^{th}, and 36^{th} month of the study. Additionally, women of child-bearing age will be administered a pregnancy test during study days 29-32, 59-62, and 89-92, according to the treatment group.

If at any time during the study, you experience any adverse event(s) or a medical problem, you should immediately contact the clinic and, if the doctor finds it is necessary, come to the clinic for evaluation. If necessary, additional blood tests and/or an electrocardiogram will be performed to evaluate and monitor the adverse event(s).

If you do not meet the study inclusion requirements, or not willing to participate, you will receive standard treatment and medical follow-up at the “Platform for the Comprehensive Care of patients with Chagas disease”.

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Participant Responsibilities

If you agree to participate, the study team will ask you for the following:

- Return to the 14, 15, or 17 weekly scheduled visits at the clinic, according to your assigned treatment group. If at some point, it is difficult to return, you must contact the nurse or the doctor to schedule a new appointment.
- Complete and bring your **study treatment journal** along with all the study medication and boxes at each scheduled clinic visit.
- Not to drink alcoholic beverages during the treatment with BZN or NFX.
- Communicate with doctors or nurses in case of any questions, problems, or questions relating to your health or your treatment.
- Women of child-bearing age, must agree to use an effective contraceptive method during the treatment period. In addition, if pregnancy occurs during the course of the treatment, study staff must be notified immediately so treatment can be stopped.

Discomfort during blood work

You may feel a slight discomfort when the blood sample is taken. It is possible (though not likely) that there is a bruise during this procedure. The medical team will do their utmost to minimize any inconvenience or discomfort. The amount of blood drawn does not cause anemia or any other health related problems.

Study medication side effects

BZN and NFX are well-known and widely used medications for the treatment of Chagas disease. Potential adverse effects of BZN include headache, skin rash, itching, generalized edema, generalized hematoma (called purpura), nausea, vomiting, abdominal pain, loss of appetite, dizziness, tiredness, muscle aches or joint tingling in extremities, and fever. Blood tests may show a decrease in white blood cells, but that is rare.

Potential adverse effects of NFX include headache, skin rash, itching, nausea, vomiting, abdominal pain, diarrhea, loss of appetite, dizziness, fatigue, insomnia, anxiety, muscle aches, tingling in extremities, and more rarely an increase in liver enzymes and shortness of breath.

If any adverse effects are experienced, the study staff should be notified and also stated at the scheduled visits.

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If an adverse effect is experienced between scheduled visits, the study staff should be notified. There are treatments (such as medication) to help overcome some of the adverse effects, and may be available to you free of charge by the doctor if he considers it necessary.

If vomiting occurs after taking the study medication, you need to contact the study staff. The next scheduled dose may be taken as directed by the study doctor.

There may be unforeseeable risks not yet known while participating in this study. You are urged to notify the study staff and/or study doctor of any adverse effects.

Benefits

As part of the study, we will evaluate if you are free of the parasite that causes Chagas disease after the study treatment. If traces of the parasite are still found in your system, you will be offered the standard treatment with the medicine (BZN or NFX) not received during the study treatment, free of charge. This alternative treatment may succeed where previous treatment has failed, but we cannot guarantee such a thing. Your participation in the study can contribute significantly to improve the use of the currently used medications used for Chagas disease and the evaluation of biomarkers to measure the effectiveness of treatments.

Study Alternatives

The decision to participate in the study is voluntary and in the event that you do not want to participate, it will not pose any effect on access to standard treatment or on the quality of care provided to you. If you decide not to participate in the study, you will receive free of charge the standard treatment for the disease of Chagas in Bolivia, and medical care in the Platform for the Comprehensive Care of patients with Chagas disease.

Confidentiality

Your identity, medical data and participation in the study is strictly confidential. For example, your name will not appear with any study information, except in the clinic. At the end of the study, a report will be written about the results and these will be published, so that doctors can learn about the treatment outcomes. This report will not include any personal information, such as your name, address or other identifying information.

By agreeing to participate in this study, you allow access of the study information to authorized medical staff, coordinators, clinical, auditors and regulatory authorities or the Ethics Committee to ensure that the study is conducted properly and ethically.

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Withdrawal

Your participation is voluntary and it is not mandatory to participate in the study. If you decide to participate, you can, at any time, change your mind, without losing any rights as a patient. Moreover, you will be informed if there is a better treatment so you may undergo it.

It is also possible that the study doctor may withdraw your participation from the study if it is believed necessary, due to safety concerns. In this case, if you wish, you may receive the standard treatment and attention for Chagas disease at the Chagas Platform.

Compensation

You will not receive any compensation for participating in the study. However, you will be reimbursed for travel expenses and/or loss of your workday wages to come to the consultations at the clinic.

If you happen to experience an injury or disease related to the study, CEADES will pay for the related treatment costs. In the rare case that you happen to experience complications due to the study medication, we will do our utmost to ensure that you receive the necessary care and treatment.

If you have a research-related illness or injury, care will be available to you as usual in the Chagas Platform, but the medical insurance provided in the study, will be responsible for the cost of treatment.

The Chagas Platform, through the medical insurance provided to all participants of the study, agrees to assume responsibility for the reasonable costs of immediate treatment of any adverse reaction or physical injury to a participant which, in the reasonable judgement of the Chagas Platform and study sponsor, specifically resulted from the study treatment and not from a pre-existing abnormal medical condition or underlying disease.

Contact Information

For more information, or in case of any problems associated with the study, please contact:

Cochabamba:

Dr. Faustino Torrico, M.D., Plataforma Chagas, Av. Aniceto Arce y Av. Oquendo, Cochabamba, Tel: (4)423-0009 (office) and 77411905 (cellular), e-mail: foxtorrico@yahoo.com

Dr. Jimy Pinto, M.D., Plataforma Chagas, Av. Aniceto Arce y Av. Oquendo, Cochabamba, Tel: (4)466-2381 (office) and 65775830 (cellular), e-mail: jimymed@hotmail.com

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Sucre:

Dr. Wilson Garcia, M.D., Plataforma Chagas, Avenida Japón, 14, Sucre, Chuquisaca, Bolivia. Tel.: (4)641-4068; e-mail: wigaru@gmail.com

Tarija:

Dr. Lourdes Ortiz, M.D., Plataforma Chagas, Calle España esquina Pasaje California (Zona El Tejar), Tel.: (4)667-2252, e-mail: lourdesortizd@yahoo.es

If you have any questions related to your rights as a patient, please contact:

Dr. José Pedro Ribera, M.D., CEADES Ethics Committee President, Street Rico Toro 1054, Cochabamba, Tel 71744155, e-mail: huacaraje72@gmail.com

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Sample Collection

Blood and urine samples collected during the study will be used to assess healing of Chagas disease and to monitor the functioning of the liver and kidneys. We also request your permission to store your remaining blood samples, including serum and/or plasma, and urine samples for further studies related to Chagas disease. These samples will not be used in human genetic studies. All samples will be kept for 10 years after the end of the study and the results of their analysis will be confidential.

- ❑ Yes, I grant permission for any remaining blood samples, including serum and/or plasma, and urine samples, to be stored and used for further studies related to Chagas disease.

- ❑ No, I **DO NOT** grant permission for any remaining blood samples, including serum and/or plasma, and urine samples, to be stored or used for further studies related to Chagas disease.

A copy of this document will be provided to the patient.

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INFORMED CONSENT FORM

Place of study: Chagas disease clinic located in Cochabamba, Tarija, and Sucre, Bolivia.

Study Title: New Chemotherapy Regimens and Biomarkers for Chagas Disease

Study Investigators: Dr. Faustino Torrico (CEADES, Cochabamba, Bolivia), Dr. Joaquim Gascón (ISGlobal, Barcelona, Spain), and Dr. Igor C. Almeida (University of Texas at El Paso, El Paso, TX, U.S.A.)

I have read the information on this form or I have been read this form in a language that I understand. I have had the opportunity to ask all questions regarding the study and these have been answered satisfactorily. I know that I can refuse or leave the study without any prejudice or loss of benefits or services to me or my family. I agree to participate in the study. By signing this form, I agree that all individual data collected during the course of the study are accessible to investigators, monitors, auditors, and, committees of ethics or regulatory authorities.

Patient Name (print): _____

Patient Signature: _____ **Date**: _____

Principal Investigator: _____

Principal Investigator Signature: _____ **Date**: _____

If the patient is illiterate, the presence of an impartial witness throughout the consent process is required.

Witness (if applicable):

Name: _____

Signature: _____ **Date**: _____

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