

Safety and Tolerability of Metformin in People with Tuberculosis (TB)
and Human Immunodeficiency Virus (HIV) (METHOD)

NCT04930744

Main Informed Consent-Form 2

Document Date: 19 August 2024

PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT TO TAKE PART IN A RESEARCH STUDY

Each participant should receive, read and understand this document
before any study-related procedure is conducted.

STUDY CODE: AUR1-1-199

STUDY TITLE: A Prospective, Randomized Open-Label Phase II Study of the Safety and Tolerability of Metformin in Combination with Standard Antimicrobial Treatment of Pulmonary Tuberculosis in People Co-infected with HIV

FUNDER: National Institutes of Health, National Institute of Allergy, Immunology and Infectious Disease, Division of AIDS

SPONSOR: THE AURUM INSTITUTE

INVESTIGATOR: (Name of Investigator)

INSTITUTION: (Name of Institution)

STUDY SITE CONTACT DETAILS:

AFTER HOURS: 000 000 0000

DAYTIME TELEPHONE NUMBER(S): 000 000 0000

To the potential Participant: *This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.*

(This Information Sheet will be available in local languages)

PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT TO TAKE PART IN A RESEARCH STUDY

Study Participation

Good day, my name is (Insert name of study staff), I work at (Insert name of Institution/Department). I would like to **invite** you to consider participating in a research study, entitled ***“A Prospective, Randomized, Blinded Phase 2A Study of the Safety and Tolerability of Metformin in Combination with Standard Antimicrobial Treatment of Pulmonary Tuberculosis in People Co-infected with HIV”***

- Before agreeing to participate, it is important that you read and understand the following explanation of the purpose of the study, the study procedures, benefits, risks, discomforts, and precautions as well as the alternative procedures that are available to you, and your right to withdraw from the study at any time.
- This information leaflet is to help you to decide if you would like to participate. You need to understand what is involved before you to take part in this study.
- If you have any questions, do not hesitate to ask me.
- You should not agree to take part unless satisfied about all the procedures involved.
- You may not participate in another investigational medicine research study, nor take any other investigational medicine during your participation in this study.
- Please be open with me regarding your health history, since you may be at risk by participating in this study.
- If you to take part in this study, you will be asked to sign this document to confirm that you understand the study. You will be offered a copy to keep.
- If you have a personal doctor, please discuss with or inform him/her of your possible participation in this study. If you wish, I can also notify your personal doctor in this regard:

**Participant
Initials:**

Date:

(dd/mm/yyyy)

- ☐ **YES**, I want you to inform my personal doctor / specialist of my participation in this study.
- ☐ **NO**, I do not want you to inform my personal doctor / specialist of my participation in this study.
- ☐ **I do not have** a personal doctor / specialist.

This form gives you information about a research study that will also be discussed with you. This study will examine whether by adding metformin to TB medicines you will take, if damage to the lung might be reduced and if the TB germ may be cleared more quickly. Once you have had all of your questions about the study answered, and if you agree to be in the study, you will be asked to sign this form. You will be offered a copy of this form to keep. Participation in the trial is voluntary and you may refuse to participate or withdraw from the trial at any time without penalty or loss of benefits to which you are entitled to.

The study is supported by a grant from the U.S. National Institutes of Health to The Aurum Institute, The University of Massachusetts Medical School and the Singapore Immunology Network. This research study is being conducted by The Aurum Institute and The Isango Lethemba TB Research Unit.

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The following sections describe the research study. Before you decide to take part, please take as much time as you need to ask questions with the study team, with your family, friends, or with your personal doctor / specialist or other healthcare professionals. The study team will answer any questions you have before you make a decision.

1. WHAT IS THE PURPOSE OF THE STUDY?

You are being asked to take part in this research study because you are sick from the germ called tuberculosis (TB).

TB is a type of lung infection or sickness that causes fever, cough and phlegm (sputum). Sputum or phlegm is the stuff you cough up from your lungs when you have the TB germ. If not treated, TB can cause serious illness and sometimes death. TB is different from other infections because even when TB can be treated with standard TB medicines (called drug-sensitive TB), it requires at least 6 months of treatment with a couple anti-TB medicines for cure. In addition, even when TB is cured, it can leave behind damage to the lung that can cause coughing and shortness of breath.

This study will examine whether by adding a medicine called **metformin** to TB medicines, damage to the lung might be reduced and the infection might be cleared more quickly. Metformin is not an antibiotic. It does not directly kill the germ that causes TB. The study will evaluate the safety of these drugs taken together – that is to find how often mild or severe side effects might occur when taking metformin with TB drugs and whether taking metformin would interfere with being able to take the TB drugs each day by causing side effects. Metformin will be compared to the standard TB medicines given without metformin. When you enrol in the study, you will have an equal chance of being the group that takes standard TB medicines alone or with the addition of metformin. This means that you have a chance (**like flipping a coin**) of 1 in 2 (50% chance) to be put on the following medicines:

- 1- Standard TB medicines (Isoniazid, Rifampicin, Ethambutol and Pyrazinamide) **only**
- 2- Standard TB medicines (Isoniazid, Rifampicin, Ethambutol and Pyrazinamide) **and metformin**

Which treatment you will get, will be determined by chance. All of the 112 participants in this study will receive standard TB medicines. Of the 112 participants in this study, 56 will also get metformin.

You have been invited to participate in this study because you have drug-sensitive TB and you also have HIV. Your type of TB can usually be cured with standard TB medicines, if they are taken as directed for a full 6 months. Your joining this study will help increase knowledge about treating drug-sensitive TB. Participating in this study will also mean that you will receive closer medical attention that otherwise might not be available.

Your participation in this study will last 36 weeks. All the participants in this study will receive anti-TB drug treatment for 24 weeks. Metformin will be given for 11 weeks, beginning one week after standard TB medicines are started. Some participants will receive metformin added to standard TB medicines while others will receive standard TB medicines without metformin. Which treatment each patient will get will be determined by chance, like tossing a coin. Metformin will be started 1 week after starting standard TB medicines.

Some participants will receive a medicine called **metformin**, which is an approved medicine to treat diabetes. Metformin does not usually lower blood sugar in people who do not have diabetes and is sometimes used to treat conditions other than diabetes. While millions of people have been treated with metformin, the use of metformin in TB treatment is investigational. This study will find out if metformin can help with lung damage and swelling (inflammation) when you have TB.

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Participants who will take metformin will start the drug by **1 tablet every day with the first meal of the day**, beginning 1 week after the start of standard TB medicines. After 1 week, the **dose of the metformin tablet will increase to one tablet twice each day, taken with meals**.

Anti-TB treatment will include 4 medicines every day for the first 2 months. These medicines are isoniazid, rifampicin, pyrazinamide, and ethambutol. After that, all participants will take isoniazid and rifampicin every day for 4 more months. **Isoniazid will be 1 pill each day. Rifampicin will be 2 pills every day. The number of pyrazinamide and ethambutol pills will depend on how much you weigh.** A study nurse will help you keep track of all the pills so that you can take them every day as directed. These are the standard treatments given to all TB patients.

All participants will take **1 pill of vitamin B6 every day during TB treatment**. This will prevent low levels of this vitamin in the body, which can be caused by isoniazid.

2. HOW MANY OTHER PEOPLE WILL BE IN THE STUDY?

There will be approximately 112 people aged between 18 and 65 years of age who will be enrolled in this study.

3. HOW LONG WILL PARTICIPATION IN THE STUDY LAST?

If you meet the study requirements and decide to join, you will be in this study for approximately 9 months.

4. WHAT WILL HAPPEN BEFORE THE RESEARCH STUDY BEGINS?

If you decide to take part in this study, we will ask you to sign this consent document before we do any study-related activities.

5. STUDY TESTS AND PROCEDURES

If you decide to participate in this study, we will ask you to come to this clinic for screening and 14 study visits one final interview by phone. Different types of tests and procedures will be performed at each study visit. These will include:

- a. Information about your background, medical history, medications, and symptoms will be obtained.
- b. Physical examinations will be performed.
- c. Blood will be obtained to monitor safety, to check levels of the medicines you have been taking, and to see if treatments are having the desired effects on the bacteria and on your immune system. We will also ask your permission to store blood to use for other tests to see how your body handles the study drug and how the study drug helps your immune system fight TB. The total volume of the blood we will draw will be about 154 mL, or about 27 teaspoons. On average, this is about 14 mL (3 teaspoons) per visit. On some visits, more blood will be obtained, and on other visits, a smaller amount (or no blood) will be obtained.
- d. A drop of blood will be obtained by fingerprick to measure blood sugar.
- e. Sputum (phlegm) will be obtained to see if the TB germ is being eliminated. We will ask you to try to provide a sputum specimen every time you come to clinic.
- f. Tests will be performed to take pictures of your lungs. These will include 1 chest X-ray when you start TB treatment, 1 chest X-ray when you finish TB treatment. The X-rays will be taken at **[Insert Institution]**, nearby the research site. We will drive you to the hospital and bring you back here when the X-ray is done. The test will allow us to see how the Host Directed Therapy (HDT) medicines may help in reducing the inflammation (swelling) in the lung.

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- g.** Breathing tests will be performed. These will require that you breathe out quickly into a cardboard tube. We will measure how rapidly the air moves out of your lungs. This takes about 10 minutes.
- h.** Walking tests will be performed. These will indicate how far you are able to walk in 6 minutes.

6. WHAT WILL HAPPEN DURING THE RESEARCH STUDY?

a. Screening Visit

The study will begin with a screening visit. The purpose of the screening visit is to find out if you meet all the requirements to take part in this research study. The screening visit may take about 3 to 4 hours.

During the screening visit, you will be asked to have the following tests and procedures:

- The study doctor or staff will screen you for COVID-19 symptoms, contact history and recent activities with increased risk for exposure. If you present with a confirmed COVID-19 diagnosis or high suspicion of COVID-19, you will be ineligible for participation.
- The study doctor or staff will ask you about your medical history and review medications you are taking.
- You will have a physical examination completed.
- Your height, weight, blood pressure, heart rate, and body temperature will be recorded.
- Blood will be collected to assess your general health. If you are a woman and could become pregnant, urine samples will be collected for pregnancy tests. A blood sample will also be used to check if you have hepatitis (liver infection) and to confirm for HIV infection and CD4 count.
- A chest X-ray will be performed.

By the end of the screening visit, the study doctor might determine that you will not be asked to join the study. The study doctor will explain why and will discuss with you other treatment options. By the end of the screening visit, the study doctor might determine that you could be asked to join the full study and you will be invited to return to the clinic in 2 or 3 days to review the blood test results.

b. Enrollment and baseline (Week 0)

Before you are asked to join the study, the study doctor will review the chest X-ray and blood tests sent from the screening visit. Based on the screening blood tests, the study doctor might determine that you will not be asked to join the study. The study doctor will explain why and will discuss with you other treatment options. If the study doctor determines that the screening tests show you can join the study then you will be offered enrollment, which you can accept or decline as you wish. If you enroll in the study:

- You will be asked about any medications you have taken and about any symptoms (side effects or other problems) that have occurred since your last visit.
- You will have a physical examination completed.
- Your blood pressure, heart rate, and body temperature will be recorded.
- You will have an ECG.
- You will have a sputum sample collected.
- Blood and samples will be taken to assess HIV viral load and immune function
- You will complete a list of questions about how well you are breathing.
- You will have a breathing test performed.
- You will have a test to see how far you can walk in 6 minutes.
- You will begin receiving standard TB medicines.

You will be asked to return to the clinic one day after the enrollment visit to repeat the breathing test.

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c. Treatment (Week 1)

- You will be asked about any symptoms (side effects or other problems) that you may be experiencing.
- You will have a physical examination completed.
- Your weight, blood pressure, heart rate, and body temperature will be recorded.
- Your blood sugar will be measured by fingerprick.
- You will have a sputum sample collected.
- If you are assigned to metformin treatment, you will start taking 1 tablet daily with the first meal of the day.

d. Treatment (Week 2)

- You will be asked about any symptoms (side effects or other problems) that you may be experiencing.
- You will be asked about the medicines you have been taking.
- You will have a physical examination completed.
- Your blood pressure, heart rate, and body temperature will be recorded.
- Your blood sugar will be checked by fingerprick.
- You will have a sputum sample collected.
- If you are assigned to metformin treatment, you will start taking the tablet twice daily with meals.

e. Treatment (Weeks 3, 4)

- You will be asked about any symptoms (side effects or other problems) that you may be experiencing.
- You will be asked about the medicines you have been taking.
- You will have a physical examination completed.
- Your blood pressure, heart rate, and body temperature will be recorded.
- Your blood sugar will be checked by fingerprick.
- You will have a sputum sample collected.
- On Week 4 only, you will have a blood sample taken to check kidney and liver function.
- On Week 4 only, if you are a woman of child-bearing potential, you may have a pregnancy test completed.

f. Treatment (Week 5)

- You will be asked about any symptoms (side effects or other problems) that you may be experiencing.
- You will be asked about the medicines you have been taking.
- You will have a physical examination completed.
- Your blood pressure, heart rate, and body temperature will be recorded.
- Your blood sugar will be checked by fingerprick.
- You will have a sputum sample collected.
- Blood samples will be taken to assess medication levels.

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g. PK (Pharmacokinetic) sampling and Whole Blood Bactericidal Assays (WBA)

(Please delete below if not applicable to your site)

- 10 Participants randomized to each of the arms will have intensive PK sampling performed at week 5.
- A maximum of 40 enrolled participants will have sparse PK blood testing done and will have an extra 3 tubes of blood drawn for a test called the WBA which measures how well your white blood cells can kill TB in the laboratory.
- A maximum of 52 participants will be enrolled and will not have the intensive pharmacokinetic blood tests and WBA tests done. They will only have sparse pharmacokinetic blood testing done.

(Please delete below if not applicable to your site)

PROCEDURES FOR INTENSIVE PHARMACOKINETIC TESTING

- You will arrive at the clinic as directed by the study team at week 5 to undergo an overnight stay in the research clinic for a series of 7 (seven blood draws. We will draw 2ml of blood 7 times over 10 hours from your arm. This is 14ml of blood or about 3 teaspoons of blood. For this visit the study team will insert a needle (called a catheter) in your arm so you do not have to be pricked every time your blood is drawn. These blood samples, called pharmacokinetic evaluations (PK), will be stored and evaluated later to measure the levels of metformin (if you get the metformin drug by chance and not the placebo drug) and also isoniazid and pyrazinamide which are part of the normal TB drugs you will receive. We will see how much of these drugs are in your body. One intensive PK evaluation will require an overnight stay in the research clinic for repeated blood draws, when you take your metformin drug at 0 hours and then again after 1 hour has passed, then again after 2 hours, then 4 hours, then 6, 8, 10 hours have passed. This means that you will stay overnight at the facility where we do these tests.
- On the day of the intensive PK evaluation, you will take your TB medicines and metformin (if you are on the metformin arm) together with water, without food. A meal will be provided after 1 hour has passed since you took your medicine. This will be the only time you take your metformin without food. All other doses of metformin should be taken with food. Please remember to report any gastrointestinal issues you may feel to the study team at any of the study visits (but as soon as possible) before the PK evaluation. You will only have one metformin tablet one this day in the morning without food, so if you have not experienced any symptoms by week 5, we do not think that taking metformin without a meal for this one dose will cause any symptoms or adverse events. If you experience any symptoms, please let your study doctor or nurse know so that they can help you and or give you some medication that may help you.
- We will take you and fetch you from these facilities and will have dedicated staff who will help and show you what is needed when. They will be there the whole night to make sure you are OK and to make sure you eat and are comfortable. We will make sure you get the food you need and are comfortable at these visits, but you should remember to bring an overnight bag with the things you need and with other medicines or tablets you may be taking. Because you need to stay overnight, you will be reimbursed for the trouble of staying overnight and for having the intensive PK sampling, to the amount of R1000. You can always withdraw your permission for us to do this test on you, but we cannot guarantee you will

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then get a slot in the next section of 92 participants because we may already have enrolled all 112 participants.

PROCEDURES FOR SPARSE PHARMACOKINETIC (PK) TESTING AND WHOLE BLOOD BACTERICIDAL ASSAY (WBA)

- You will arrive at the clinic as directed by the study team at week 5 for sparse pharmacokinetic testing, for a series of 3 blood draws. We will draw 2ml of blood 3 times over 6 hours from your arm and another 2mls at the same time points for the WBA. This is two sets of 6ml of blood (a total of 12ml which is just less than 3 teaspoons of blood). For this visit the study team will insert a needle (called a catheter) in your arm so you do not have to be pricked every time your blood is drawn. These blood samples, called pharmacokinetic evaluations (PK), will be stored and evaluated later to measure the levels of metformin (if you get the metformin drug by chance and not the placebo drug) and isoniazid and pyrazinamide which are part of the normal TB drugs you will receive. We will see how much of these drugs are in your body. One sparse PK evaluation and WBA will occur over 6 hours and you will not need to stay overnight stay in the research clinic for repeated blood draws, when you take your metformin drug or placebo. These blood draws will be taken at 0 hours and then again after 2 hours have passed and then again after 6 hours. We will make sure you are OK and to make sure you eat and are comfortable, you will be reimbursed for the trouble of staying at the clinic for 6 hours and for having the sparse intensive PK sampling with WBA, to the amount of R450. You can always withdraw your permission for us to do the WBA (which means that we will take 6ml of blood less (about 2 teaspoons less blood) on you, but we will still draw blood for the sparse pharmacokinetic testing

PROCEDURES FOR SPARSE PHARMACOKINETIC(PK) TESTING ONLY

- You will arrive at the clinic as directed by the study team at week 5 for sparse pharmacokinetic testing for a series of 3 blood draws. We will draw 2ml of blood 3 times over 6 hours from your arm.. This is for one set of 6ml of blood or about more 1 teaspoon)of blood. For this visit the study team will insert a needle (called a catheter) in your arm so you do not have to be pricked every time your blood is drawn. These blood samples, called pharmacokinetic evaluations (PK), will be stored and evaluated later to measure the levels of metformin (if you get the metformin drug by chance and not the placebo drug) and isoniazid and pyrazinamide which are part of the normal TB drugs you will receive. We will see how much of these drugs are in your body. One PK evaluation will occur over 6 hours and you will not need to stay overnight stay in the research clinic for repeated blood draws, when you take your metformin drug or placebo. These blood draws will be taken at 0 hours and then again after 2 hours have passed and then again after 6 hours. We will make sure you are OK and to make sure you eat and are comfortable., you will be reimbursed for the trouble of staying at the clinic for 6 hours and for having the sparse intensive PK sampling only, to the amount of R450. We will not be drawing blood for the WBA testing. You can always withdraw your permission for us to do the sparse testing but that will mean that you will not be able to enter the study. If you agree and we draw your blood and then you ask us to not use the information we get from your blood, that is fine but we will still like to carry on looking to check you are still safe until your time on the study finishes later on in the future.

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h. Treatment (Weeks 6, 7)

- You will be asked about any symptoms (side effects or other problems) that you may be experiencing.
- You will be asked about the medicines you have been taking.
- You will have a physical examination completed.
- Your blood pressure, heart rate, and body temperature will be recorded.
- Your blood sugar will be checked by fingerprick.
- You will have a sputum sample collected.

i. Treatment (Week 8)

- You will be asked about any symptoms (side effects or other problems) that you may be experiencing
- You will be asked about the medicines you have been taking.
- You will have a physical examination completed.
- Your blood pressure, heart rate, and body temperature will be recorded.
- Your blood sugar will be measured by fingerprick.
- You will have a sputum sample collected.
- If you started HIV treatment for the first time during this study, a blood sample will be taken to assess HIV viral load. If you are a woman of child-bearing potential, you may have a pregnancy test completed.
- Blood samples will be taken to assess kidney, liver, and immune function.

j. Treatment (Week 10)

- You will be asked about any symptoms (side effects or other problems) that you may be experiencing
- You will be asked about the medicines you have been taking.
- You will have a physical examination completed.
- Your blood pressure, heart rate, and body temperature will be recorded.
- Your blood sugar will be measured by fingerprick.
- You will have a sputum sample collected.

k. Treatment (Week 12)

- You will be asked about any symptoms (side effects or other problems) that you may be experiencing
- You will be asked about the medicines you have been taking.
- You will have a physical examination completed.
- Your blood pressure, heart rate, and body temperature will be recorded.
- Your blood sugar will be measured by fingerprick.
- You will have a sputum sample collected.
- If you are a woman of child-bearing potential, you may have a pregnancy test completed.
- If you were assigned to metformin treatment, you will stop taking it.
- You will complete a list of questions about how well you are breathing.
- You will have a breathing test performed.
- You will have a test to see how far you can walk in 6 minutes.

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l. Treatment (Week 16)

- You will be asked about any symptoms (side effects or other problems) that you may be experiencing
- You will be asked about the medicines you have been taking.
- You will have a physical examination completed.
- Your blood pressure, heart rate, and body temperature will be recorded.
- You will have a sputum sample collected.
- Your blood sugar will be measured by fingerprick. If you are a woman of child-bearing potential, you may have a pregnancy test completed.
- Blood samples will be taken to assess viral load, kidney, liver, and immune function.

m. End of treatment (Week 24)

- You will be asked about any symptoms that you may be experiencing
- You will be asked about the medicines you have been taking.
- You will have a physical examination completed.
- Your blood pressure, heart rate, and body temperature will be recorded.
- You will have a sputum sample collected.
- Blood and samples will be taken to assess immune function.
- You will have a sputum sample collected.
- If you are a woman of child-bearing potential, you may have a pregnancy test completed.
- You will complete a list of questions about how well you are breathing.
- You will have a test to see how far you can walk in 6 minutes.
- You will have a breathing test performed.
- You will have a chest X-ray performed.
- You will stop taking TB medicine.

n. End of Study (Week 36)

- You will be contacted by phone and asked about any symptoms that you may be experiencing

7. HOW WILL I RECEIVE THE METFORMIN?

You will receive all medicines as tablets from study team.

8. WHAT HAPPENS WHEN I FINISH TAKING THE METFORMIN?

You will finish taking the study drug at week 12.

9. WHAT HAPPENS WHEN I FINISH TAKING ANTI-TB DRUGS?

You will finish taking the anti-TB study drug at week 24. Twelve weeks later you will be contacted for a telephone interview.

10. WHAT ARE THE RISKS AND POSSIBLE DISCOMFORTS OF BEING IN THIS RESEARCH STUDY?

Any research has some risks, which may include things that could make you sick, make you feel uncomfortable, or hurt you. You might experience negative effects related to the study drug while participating in the study. All research participants taking part in the study will be watched carefully for any side-effects; however, the study team does not know all the effects that the study drug may have on you. The study team may give you medicines to help reduce the side-effects. These effects may be mild

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or serious. In some cases, these effects can be long lasting, or permanent, and may even be life threatening, but we will watch very carefully for all side-effects for your safety.

10.1 For metformin:

Adverse events most commonly reported with the study drug included gastrointestinal disorders (poor appetite, abdominal pain, discomfort, and diarrhea). These symptoms usually improve even if you keep taking the drug. Metformin can also cause low blood sugar in some people. This results in symptom of weakness, dizziness, sweating, or fainting. If the blood sugar is critically low it can result in seizures (fits) and death. Metformin has very rarely been reported to cause an imbalance of blood chemistry called acidosis that can be life-threatening. You will be monitored carefully for these and other symptoms during this study. You should get medical help and contact your study doctor right away if you think you have any of the following symptoms of a serious chemical imbalance: nausea (upset stomach), vomiting, shortness of breath, or feeling unusually tired or weak.

All medicines have a potential risk of an allergic reaction, which if not treated promptly, could become life threatening. You should get medical help and contact your study doctor right away if you think you have any of the following symptoms of a serious allergic reaction: trouble breathing, or swelling of the face, mouth, lips, gums, tongue or neck. Other allergic reactions may include rash, hives, or blisters.

Metformin use in men around the time of conception can increase the risk of birth defects in male babies. The risk was not apparent if metformin exposure occurred the year before or the year after conception, so it seems to self-resolve without sequelae / consequences. The most common defects were genital abnormalities in males, but the risk seems small. If you are a male who is participating in the study, it is important that you understand that there is a small risk that if you are taking metformin at time of conceiving, that metformin can affect the spermatogenesis process (the process of making sperm in the testes).

For this reason, it is important that you make use of condoms and encourage your heterosexual partner(s) to use contraception. Metformin will be administered for 11 weeks and the spermatogenesis process can take up to three months therefore, male participants wishing to participate in the trial must be willing to use condoms for a period of 3 months **after** completing metformin adjunctive host directed therapy. This will only affect male participants who are enrolled into the metformin arm.

Contraception use should continue for a full 24 weeks from when you start taking metformin. We can assist in either providing contraception for your heterosexual partner(s) or referring your heterosexual partner(s) for contraception if you would like us to.

It is important that you report all symptoms and side effects that you experience as soon as they occur, whether or not you think they are caused by the study drug. The phone numbers for the study team are on the first page of this document.

10.2 For anti-TB medicines:

Each of the anti-TB drugs can cause adverse effects. These can include hepatitis of the liver (nausea, abdominal pain, lack of appetite, yellow coloration of the skin), low blood counts, body aches, and trouble with color vision. Routine testing can help prevent serious problems from these effects. You will be monitored to help prevent them in this study. In addition, it is important to note that if you are female and on pregnancy prevent contraceptive pill or the injection, one of the anti-TB drugs (Rifampin) can make your contraception less strong and this may mean that you can fall pregnant even though you are on pregnancy prevention medicine. It is important that you discuss this with your partner and always use a male or female condom during sexual intercourse to ensure you do not fall pregnant.

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Risks and possible discomforts you might experience from the study procedures include:

- **Blood Draw:** A blood draw may cause faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight chance of infection. The risk is reduced because qualified and experienced study team members will be drawing your blood.
- **Chest X-ray:** Chest X-rays require brief exposure to a small amount of radiation equal to about 10 days of the background radiation that everyone is exposed to every day. Radiation in very large doses can interfere with blood cells and can cause cancers. However, the dose used in this study is so small that there is very small risk to you.
- **Breathing tests:** Vigorous breathing may cause brief coughing spells.

10.3 Other Risks

While the placebo contains no active drug, some people taking placebo during research studies have symptoms similar to drug side effects. During the study you will not know if you are taking metformin or placebo. **It is important that you report all symptoms and side effects that you experience as soon as they occur, whether or not you think they are caused by the study drug.**

Metformin is not known to cause birth defects in a baby but pregnant women may be at higher risk for side effects of metformin. For this reason, women of childbearing potential are excluded from participating in this study unless they use birth control. The study doctor will discuss this with you during screening. If nonetheless you have reason to believe that you have become pregnant during the course of the study, you must discuss this with the study doctor immediately. If you are breast feeding a baby, you will also not be able to be in the study.

11. ARE THERE ANY SPECIAL INSTRUCTIONS TO FOLLOW WHILE PARTICIPATING IN THIS STUDY?

During this study, it is important that:

- You do not consume grapefruit, grapefruit juice, or grapefruit-related citrus fruits (e.g., Seville oranges, pomelos) during this study (7 days before and while taking study drug).
- There may be certain medication and herbal supplements that you should not take while participating in this study. Your study doctor will review what medications you are currently taking. Please notify your study doctor if you begin taking anything new while you are participating in this study and also inform your doctor / specialist that you are participating in a drug trial for the study drug (you can ask your physician to contact the Principal Investigator for any further details).
- Tell a study doctor immediately if you have any symptom, complaint, or injury. If you seek emergency care or if hospitalisation is required at any time during the study, please tell the treating doctor that you are enrolled in this research study and that study personnel must be informed promptly.
- You must take the study drug with your evening meal to reduce the chance of low blood sugar. If you have symptoms of weakness, dizziness or sweating that might be due to low blood sugar you should drink a cup of a sugary soft drink or orange juice before doing anything else and then tell the study doctor so you can be checked.

12. WHAT OPTIONS ARE AVAILABLE OTHER THAN BEING IN THIS STUDY?

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You do not have to be in this study to receive treatment for your TB. Instead of taking part in this study, you may choose to receive treatment with the standard anti-TB medicines approved for use in South Africa. The risks associated with standard anti-TB medicines are mentioned earlier in this document. These are approved treatments that are effective in treating drug-sensitive TB.

13. WHAT ARE POSSIBLE BENEFITS OF BEING IN THIS STUDY?

Subjects in this study will benefit from careful medical care, including testing for drug-resistant TB. It is possible that your condition or health may improve because of study treatment or because of your visits to the research site. However, there is no guarantee that you will benefit in any way. Information from this study may help other people in the future.

14. WHAT HAPPENS IF I AM INJURED AS A RESULT OF TAKING PART IN THIS RESEARCH STUDY?

If you experience a research injury, emergency medical treatment will be provided at no cost to you. A research injury is any physical injury, illness or disability caused by:

- a. administration of metformin; or
- b. any study procedure that would not have occurred but for your inclusion in the study.

If you agree to be in this study, you will be under the care of study doctors who are experts in treating TB and HIV, and you will remain in the care of your doctors in the TB and HIV clinics. You will not be charged for any of the tests or medicines used in this study. You will be reimbursed for each day that you are to come to the site for the study.

You must notify the study doctor immediately of any complications, side effects and/or injuries during the study and the nature of the expenses to be covered.

If a research related injury occurs, you have not waived any of the legal rights which you otherwise would have as a participant in this study by signing this form.

Further detailed information on the payment of medical treatment and compensation due to injury can be obtained from the study doctor. The study doctor has a copy of the Association of the British Pharmaceutical Industry (ABPI) Guidelines and the Insurance Certificate should you wish to review them.

The insurance does not cover and The Aurum Institute will not pay for:

- Medical treatment of **other** injuries or illnesses not related to administration of the study medication or study.
- Injury caused by non-observance of the protocol by study doctor and/or the participant.

15. IS BEING IN THE STUDY VOLUNTARY?

Yes. Taking part in this research study is up to you. You may choose not to take part or you can change your mind and withdraw (drop out) later. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

We will tell you if we learn new information that could change your mind about taking part in this research study. If you want to drop out, you should tell us. We will make sure you can end the study in the safest way. We will also talk to you about follow-up care, if needed.

The study doctor or the study sponsor may decide to take you out of the study without your agreement if:

- You do not follow the directions of the study team;

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- The study doctor decides that the study is not in your best interest;
- The study is stopped by the study sponsor, the institutional review board (IRB) or independent ethics committee (IEC) (a group of people who review the research to protect your rights), or by a regulatory agency;
- You become pregnant, intend to become pregnant or are nursing a child during this study.

If you leave the study for any reason, the study doctor may ask you to have one or more of the tests listed in Section 6 for your safety. The study doctor may also ask if you wish to take part in the follow up portion of the study. If you agree to continue with the follow up portion of the study, information about your health will continue to be collected. The study doctor will discuss with you the different withdrawal options.

If you withdraw or are removed from the study, blood samples that have been collected from you can be withdrawn if they have not yet been analyzed or destroyed. If you want your samples withdrawn, you should tell the study team before or at the time you leave the study.

16. WHAT WILL I HAVE TO PAY FOR IF I TAKE PART IN THIS RESEARCH STUDY?

The site will cover the cost of all examinations, tests, treatments, and procedures listed in this consent document, including condoms. The study will not cover the costs of methods other than condoms and IUD to prevent pregnancy (contraception). If you wish for the IUD to be removed after completion of the study, we will assist you to have this done at no cost to you. If you desire other types of contraceptives, you may seek medical care for this elsewhere, at either private or public healthcare facilities. Any costs for these other types of contraceptives will be your responsibility.

You may need to receive medical care that is not listed in this document. The site will not cover the costs of that care unless it is needed to treat a research injury (see the discussion of research injury, above).

The study drugs will be provided free of charge while you are participating in this study.

17. WILL I BE PAID FOR TAKING PART IN THIS STUDY?

You will not be paid to participate in this study, but your transport and out-of-pocket expenses will be reimbursed R300 per standard visit for your time, inconvenience and expenses. You will be reimbursed R450 at V06 (week 5) for sparse PK sampling and WBA that may take up to 6 hours.

(Please delete below if not applicable to your site)

If you are doing intensive PK sampling (20 participants randomly selected), you will be reimbursed R1000 per night at V06 (week 5) as this will be an overnight stay at **[Insert Site Name]**. Please discuss this with the study team if you require any further information.

18. ABPI STATEMENT ON COMPENSATION:

The Aurum Institute (The Sponsor) will provide compensation for reasonable medical expenses incurred as a result of study-related injury or illness, determined according to the guidelines laid down by the Association of the British Pharmaceutical Industry (ABPI Guidelines), and Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa.

- You must notify me immediately of any complications, side effects and/or injuries during the study and the nature of the expenses to be covered.
- If a research related injury occurs, you have not waived any of the legal rights which you otherwise would have as a participant in this study by signing this form.

Further detailed information on the payment of medical treatment and compensation due to injury can

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be obtained from me. I have a copy of the ABPI Guidelines (2014) and the Insurance Certificate, should you wish to review them.

The insurance does not cover and the sponsor will not pay for:

- Medical treatment of other injuries or illnesses
- Injury caused by non-observance of the protocol

I am indemnified by the sponsor conditional upon:

- My compliance with the applicable requirements of the study protocol
- My compliance with the regulations of the South African Health Products Regulatory Authority and the University of the Witwatersrand, Human Research Ethics Committee (HREC).
- The handling and administration of the study medication in accordance with instructions and guidelines provided in the protocol, subsequent amendments and related documents
- The indemnification is not intended to be and is not a substitute for my personal malpractice insurance.

Please note that if you have a life insurance policy you should enquire whether your insurance company requires notification of your intention to participate in a clinical study. Information to date is that it should not affect any life insurance policy taken out. Nevertheless, you are strongly advised to clarify it with the company concerned.

YOUR RIGHTS UNDER ANY APPLICABLE DATA PROTECTION LAWS ARE NOT AFFECTED.

19. CONFIDENTIALITY (KEEPING YOUR INFORMATION SECRET)

Your doctors, of course, will know who you are and about your TB. Because we are going to record some information about you and how you respond to the medicine, there is a small risk that you would lose some privacy about your HIV-serostatus and your TB. Representatives from different agencies will be reviewing the information that we collect, and they may see your name. This is not likely because we will only be recording your name on one sheet of paper, and that paper will be kept in a locked place, and only people directly involved in this study will see that paper. The other people involved in this study will only see your information identified as a number. These are the agencies involved in this study:

- This information will be reviewed by authorised representatives of **The Aurum Institute and the Isango Lethemba TB Research Unit.**
- The information might also be inspected by the **University of the Witwatersrand, Human Research Ethics Committee (HREC)**, the **South African Health Products Regulatory Authority (SAHPRA)** and/or the **National Institutes of Health (United States)**, the **South African National Clinical Trials Register (SANCTR)**, as well as your personal doctor. Therefore, you hereby authorise me to release your medical records to The Aurum Institute or the Isango Lethemba TB Research Unit, its employees or agents, domestic and foreign regulatory health authorities, the South African Health Products Regulatory Authority and the University of the Witwatersrand, Human Research Ethics Committee (HREC).
- These records will be utilised by them only in connection with carrying out their obligations relating to this clinical study.
- Any information uncovered regarding your test results or state of health as a result of your participation in this study will be held in strict confidence. You will be informed of any finding

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of importance to your health or continued participation in this study but this information will not be disclosed to any third party in addition to the ones mentioned above without your written permission. The only exception to this rule will be cases of communicable diseases where a legal duty of notification of the **Department of Health** exists. In this case, you will be informed of my intent to disclose such information to the authorised state agency.

- Your data will be collected, processed and stored according to the South African Protection of Personal Information (POPI) Act of 2013.

When the study is complete, we may also share study data to make it available to other researchers. Your name will not be included in this shared data. We will also remove additional information that might be used to identify you, such as your birthdate or area of residence.

If applicable for your site, any questions or concerns you may have regarding your Data Protection, you may contact the Data Protection Officer for the site, **(contact person):**
at Tel (contact number):

If you have any complaints regarding the protection of your information in this study, you may submit such complaints to the Data Protection Officer for the site, on the abovementioned contact details.

You also have a right to report any data protection complaint to the Information Regulator for your country, if applicable. The Information Regulator for South Africa may be contacted on the below details:

POPIAComplaints@inforegulator.org.za or enquiries@inforegulator.org.za

20. WHERE CAN I FIND ADDITIONAL INFORMATION ABOUT THIS RESEARCH STUDY OR THE RESEARCH RESULTS?

The Aurum Institute studies are registered on www.clinicaltrials.gov and the South African National Clinical Trials Register and the results will be posted on <http://www.clinicalstudyresults.org>. It may be many years; however, before research results are posted. Information that is posted to these websites will not include any personal information about you.

21. ETHICAL APPROVAL

- This clinical study protocol has been submitted to the **University of the Witwatersrand, Human Research Ethics Committee (HREC)** and written approval has been granted by that committee.
- The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.
- This study is funded by **National Institute of Health (United States)** and the sponsor is **The Aurum Institute**.
- I do not have any financial or personal interests with this organisation that may bias my actions.

22. WHO SHOULD I CONTACT ABOUT MY RIGHTS OR IF I HAVE QUESTIONS?

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- If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Prof Ruff, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2301 or email: EthicsRegulatory@witshealth.co.za
- If you have questions about this trial you should first discuss them with the study doctor or the above-mentioned ethics committee. After you have consulted your study doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA) at:
The Chief Executive Officer
South African Health Products Regulatory Authority
Loftus Park, Building A, 402 Kirkness Street
Arcadia, Pretoria, 0083
E-mail: Boitumelo.Semete@sahpra.org.za
Tel: 012 501 0413
- If applicable, if you have any complaints regarding the protection of your information in this study, you may submit such complaints to the Data Protection Officer for the site, on the abovementioned contact details.
- You may also contact the Sponsor Data Protection Officer for the study, Ms Marlize Pistorius at: Tel (contact number): +27 (0) 87 135 1684 or dpo@auruminstitute.org.

23. WHAT HAPPENS IF THERE ARE INCIDENTAL FINDINGS BECAUSE OF THE STUDY INVESTIGATIONS?

Study investigations like physical examination, vital signs, urine and blood tests will be reviewed by qualified persons in the research team. There is a possibility that when they review your results, they may see an abnormality that we did not expect to see in this study. This is what is called an “incidental finding”.

It is the duty of the study doctor to inform you of any abnormalities related to your health that he/she becomes aware of during the trial. You do not have the option to decline receiving information about an incidental finding. If you want, the study doctor will give information about an incidental finding to your primary/regular doctor or he / she will refer you to an appropriate health care facility for further evaluation.

- An incidental finding may cause you to feel anxious.
- An incidental finding will be part of your medical record and it may, therefore, affect your current or future life insurance or medical aid coverage, if you have these.
- An incidental finding may also benefit you if an underlying condition of medical importance is diagnosed.

The costs for any care needed to further diagnose or treat an incidental finding would not be paid for by this research. These costs, if any, would be your responsibility.

PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT TO TAKE PART IN A RESEARCH STUDY

Notification option of your regular/primary doctor/specialist? Please indicate below, by INITIALLING in the applicable space, whether you would like your regular doctor/specialist to be notified of your participation in this study:

Initials_____ YES, I want a study doctor to inform my regular/primary doctor/specialist of my participation in this study.

Initials_____ NO, I do not want a study doctor to inform my regular doctor/specialist of my participation in this study.

Initials_____ I do not have a regular/primary doctor/specialist.

Notification option for handling of incidental findings? Please indicate below, by INITIALLING in the applicable space, how you would like incidental findings (if applicable) to be handled:

Initials_____ YES, give information about an incidental finding to my primary doctor.

Initials_____ YES, refer me to an appropriate health care facility for further evaluation

List any Questions that the participant may have together with the response/ answer given to the participant below or mark the check box if there were no questions.

☐

None

OR complete table below:

	Question	Answer
1		
2		
3		
4		
5		
6		
7		
8		

PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT TO TAKE PART IN A RESEARCH STUDY

24. CONSENT

- I hereby confirm that I have been informed by the study staff about the nature, conduct, benefits and risks of the clinical study entitled: *“Prospective, Randomized Open-Label Phase 2A Study of the Safety and Tolerability of Metformin in Combination with Standard Antimicrobial Treatment of Pulmonary Tuberculosis in People Co-infected with HIV”*
 - I have also received, read and understood the above written information (Participant Information Leaflet and Informed Consent) regarding the clinical study.
 - I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
 - In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by the sponsor or on their behalf and transmitted offshore, if required.
 - I may, at any stage, without prejudice, withdraw my consent and participation in the study.
 - I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study
 - Participation in this study is voluntary. You have the right to refuse or to withdraw at any time without any risks to your medical care.
 - “I have been given a copy of this form and know that a copy of this form will be kept in my study file. I understand that I may leave the study at any time or that the study doctors may ask me to leave the study if they feel that it would be better for me.”

POPIA COMPLIANCE

In accordance with the provisions of the Protection of Personal Information Act 4 of 2013 (as amended), I hereby consent:

- a) My personal information (hereinafter ‘data’) being collected, processed, shared and stored in accordance with the research protocol as approved by the WITS Human Research Ethics Committee (Medical);
- b) To my anonymised data being shared, processed and transferred by third parties and between third parties, and where relevant beyond the jurisdictional borders of South Africa;
- c) To all findings and results flowing from my anonymised data being broadly shared and published on the conclusion of the research.

Participant's Name (print)

In full as per **ID Document**

Participant's

signature/mark/thumbprint

Date

Time

TRANSLATOR (If applicable):

Translator's Name (print)

In full as per **ID Document**

Translator's signature

Date

Time

**PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT TO TAKE PART
IN A RESEARCH STUDY**

WITNESS (If applicable):

Witness' Name (print)

In full as per **ID Document**

Witness signature

Date

Time

STUDY STAFF

I, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

Name of Study staff member obtaining
consent (print)

Study staff signature

Date

Time

PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT TO TAKE PART IN A RESEARCH STUDY

SUPPLEMENTARY INFORMED CONSENT FOR WOMEN OF CHILDBEARING POTENTIAL

☐ Applicable

☐ Not Applicable

- I understand that as I am a woman of childbearing potential and to participate in this study, I should not be pregnant or breastfeeding.
- If I am sexually active, I must use a barrier method of birth control (male or female condoms or diaphragms or cervical cap) PLUS one other effective method as indicated below:
 - subdermal implant
 - intrauterine device or intrauterine system
 - combined estrogen and progesterone oral contraceptive
 - injectable progesterone
 - contraceptive vaginal ring
 - percutaneous contraceptive patch
- I must have a negative pregnancy test before I can enter this study.
- I understand that the safety of the study medicine if taken during pregnancy may involve risks to me or my unborn child, should I become pregnant while receiving this medicine.
- If I should become pregnant, I will be immediately withdrawn from the study and be referred for medical care for my pregnancy. All aspects of health care related to my pregnancy and infant will be my responsibility.
- I will allow the site at which I am enrolled at, to access to my medical records and my child's medical records from the time I became pregnant.
- The study doctor and/or a member of the study staff have reviewed information on pregnancy prevention for women of childbearing potential with me.
- I understand that the medicine I will be taking may not be safe for my unborn baby and I should not become pregnant while I am participating in this study.
- I understand that I should immediately call the telephone number on the first page of this document if:
 - I am or think I may be pregnant
 - I have missed my menstrual cycle or it is late, or I have a change in my usual menstrual cycle (for example, heavier bleeding during my menstrual cycle or bleeding between cycles)
 - I should also call if I have changed or plan to change my birth control method, or if I need to take any medication not given to me by the study doctor.
- This supplementary informed consent has been explained to me to my satisfaction in my language of choice.
- I have been given the chance to ask questions and they have been answered to my satisfaction.
- I hereby voluntarily consent to participate in this study.
- I understand that I will be offered a copy of this supplementary consent form.

 Participant's Name (print)

In full as per ID Document

 Participant's

signature/mark/thumbprint

 Date

 Time

**PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT TO TAKE PART
IN A RESEARCH STUDY**

TRANSLATOR (If applicable):

Translator's Name (print) In full as per ID Document	Translator's signature	Date	Time
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WITNESS (If applicable):

Witness' Name (print) In full as per ID Document	Witness signature	Date	Time
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STUDY STAFF

I, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

Name of Study staff member obtaining consent (print)	Study staff signature	Date	Time
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