

VOLUNTEER CONSENT FORM

STUDY TITLE: A randomized, placebo controlled single and multiple dose, dose-escalation study in healthy volunteers to determine the safety, tolerability and pharmacokinetics of BI 397 given intravenously

STUDY NO: RD 587/22197

1. I confirm that I have approached Simbec Research regarding participation as a Healthy Volunteer in drug studies, and have requested that I be allowed to participate in this study.
2. I confirm:
 - i. That a full explanation satisfactory to myself has been given regarding the nature and purpose of the study.
 - ii. That I am in receipt of and have both read and understood the subject information sheets and their details regarding the duration and extent of the study and what is expected of myself as a subject.
 - iii. That disclosure, satisfactory to myself, has been made regarding possible consequences of the study including discomfort, inconvenience and risks such as ill effects on health and well being.
 - iv. That adequate opportunity has been given to question and seek further advice and that the investigator's advice has been understood to my satisfaction.
 - v. That I am free to withdraw from the study at any time for any reason whatsoever, however I agree that I will allow Simbec Research to give me a medical and laboratory check if I choose to withdraw.
3. I confirm that I have informed the investigator of:
 - i. Previous or current participation in healthy volunteer studies.
 - ii. Significant previous or present illness and details of consultations with a doctor.
 - iii. Medicines which have been or are currently being taken; and those which I expect to take during the study.
 - iv. My history of previous or present use of tobacco, alcohol and other drugs.

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4. I confirm that the investigator is authorised, confidentially:
- To consult my General Practitioner.
 - To inform my General Practitioner of my participation in this study.
 - To request that my General Practitioner disclose information about my health which may be relevant to the pending study.
 - To inform my General Practitioner of relevant and material findings regarding myself discovered in relation to the course of the study.

I declare that I have not knowingly withheld relevant information regarding my prior or current health or treatments.

5. I confirm that I will:
- Follow the reasonable instructions of the investigator.
 - Co-operate faithfully and not do anything which might be expected to affect the integrity of the study.
 - Inform the investigator immediately of any unusual or unexpected symptoms or any deterioration of well being or health during or soon after the study.
 - Not leave the Clinical Centre without the permission of a study physician.

6. I confirm that I will not restrict disclosure of the results of the study and will therefore allow:
- Disclosure of the results to the Sponsor of the study: and to the Regulatory Authorities.
 - Access to my personal and medical detail by the Sponsor and Regulatory Authorities, knowing that I will not be identified by name.

7. I confirm that the arrangements reached with the investigator are satisfactory regarding:
- Payment of around £690 to be made at the discretion of the investigator for the inconvenience of participating in and completing the single dose study.

Payment of around £1050 to be made at the discretion of the investigator for the inconvenience of participating in and completing the multiple dose study.

If I am withdrawn from the study for any medical or administrative reason or I choose to withdraw then payment will generally be on a "pro-rata" basis but will be at the discretion of the investigator.

VC2


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- ii. In the event of my suffering any significant deterioration in health or well being caused directly by my participation in the study, compensation will be paid to me.

8. VOLUNTEER

I confirm my request to participate in the study as detailed in the Subject Information Sheet and I confirm my consent to the terms as set out.

SIGNED:..... DATE:.....

9. INVESTIGATOR

I confirm that the volunteer has been provided with a Subject Information Sheet and a full consent form, and that I have explained the nature, purpose and possible risks of participation in this study to the volunteer.

SIGNED:..... DATE:.....

NAME OF VOLUNTEER: _____
(Please Print)

A NUMBER: _____ A _____

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SUBJECT INFORMATION SHEET

STUDY TITLE: A randomized, placebo controlled single and multiple dose, dose-escalation study in healthy volunteers to determine the safety, tolerability and pharmacokinetics of BI 397 given intravenously

STUDY NO: RD 587/22197

STUDY SPONSOR: Versicor Inc
34790 Ardentech Court
Fremont
CA 94555
USA

STUDY SUPERVISOR: DR T TANNER

PRINCIPAL INVESTIGATOR: DR S FEBBRARO

CONTACT FOR ASSISTANCE OR ADVICE OR IN AN EMERGENCY.

DR C L GODFREY
DR T FOX

DR N SANGHANI

TELEPHONE FREEPHONE [REDACTED]

DRUG NAME: BI 397

DRUG TYPE: Glycopeptide antibiotic

DRUG'S ROLE: BI 397 is an investigational drug which is being developed for use as an antibiotic.

Past Studies

This is the first administration of BI 397 to humans. In animal safety studies of BI 397, the key findings included damage to the liver and kidneys at the highest doses of BI 397 tested. While findings in animals do not always predict the same outcome in humans, we plan to carefully monitor your liver and kidney function throughout the trial. No animal safety studies have been conducted to test the effects of BI 397 on the foetus. For this reason, males will be required to use barrier method of contraception during and for up to 30 days after the study has ended. All women enrolled in this study must be post-menopausal or surgically sterilized.

Main side effects

This is the first administration of BI 397 to humans, therefore as yet unknown side-effects may occur, although drugs of the glycopeptide family to which BI 397 is related are known to cause both kidney damage and, to a lesser extent, hearing loss.

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The clinical study in which you have been invited to participate is entitled "A randomized, placebo controlled single and multiple dose, dose escalation study in healthy volunteers to determine the safety, tolerability and pharmacokinetics of BI 397 given intravenously". The purpose of the study is to see how well this new drug is tolerated and how safe it is. The study will also investigate the blood levels of BI 397. The study will be conducted in two parts:

Single Dose Study: Single dose administration of BI 397 (36 healthy males)

Multiple Dose Study: Daily administration of BI 397 over a 7-day period (48 healthy male and female volunteers)

You will only be able to participate in one part of the study.

PURPOSE OF THE STUDY

When our immune system is comprised or not functionally properly we are more susceptible to infection. More and more of these infections are becoming resistant to the drugs which are currently marketed to treat them. An example of such infections are those which are due to methicillin resistant *Staphylococcus aureus*, more commonly known as MRSA. Because of this increasing incidence of resistance, it has become necessary to develop new drugs which are able to fight these infections. BI 397 is one such drug which is being developed.

BI 397 is an investigational drug which means it is being tested in clinical trials but is not yet available for general use in patients. Before being tested in patients who have these infections, it is necessary to test BI 397 in healthy people. This is the first study where BI 397 has been administered in humans and our aim is to assess its tolerability and safety in healthy volunteers.

PRE-STUDY ASSESSMENTS

To participate in the single dose study you will need to be a healthy male, aged between 18 and 60 years. However, to participate in the multiple dose study you may be either male or female (post-menopausal or sterilised) but must be aged between 18 and 60 years. Whichever study you are invited to take part in, you will be required to attend the Clinical Centre of Simbec within the 14 days prior to the start of the study to have a physical examination and your medical history recorded. You will also have your blood pressure and pulse recorded and your height and weight measured. A blood sample will be taken to determine your health status (HIV antibody test, clinical chemistry and haematology). You will also be asked to provide a urine sample so that we can check your health status and test for drugs of abuse. In addition to these tests, you will also have a test to check your normal hearing level. This audiometry test involves you being exposed to different noise levels at a range of frequencies through a set of earphones. The results of these tests may influence your suitability for participation in the study.

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SINGLE DOSE STUDY

Study Summary

This part of the study involves a single dose of BI 397, which will be administered intravenously by an investigating doctor. There are six treatment groups; the first three treatment groups will be made up of 4 subjects per group, whilst the remaining five treatment groups will be made up of 8 subjects per group. The doses of BI 397 administered will start low and progress to the maximum study dose providing that the previous dose was well tolerated. The doses to be assessed are: 70mg, 140mg, 220mg, 360mg, 560mg and 900mg. You will take part in only one of these treatment groups. You will randomly be assigned to receive either the active drug (BI 397) or a placebo which does not contain any active drug. For every three subjects in your group that receive the active drug, one subject will receive the placebo. Neither yourself nor the staff at Simbec will know whether you have been administered the active drug or the placebo.

Study Procedures

If your pre-study examination is acceptable you will be asked to participate in the study. You will be asked to attend the Clinical Centre on Day -2 for a further audiometry test. Following this, you will be required to attend the Clinical Centre on the day prior to dosing (Day -1). The following procedures will then take place on Day -1: firstly, your medical history will be recorded and a physical examination will take place. An ECG will also be performed and your blood pressure and pulse will be recorded. In addition a blood sample will be taken to check your health status. You will also be asked to provide a urine sample so that we can check your health status and test for drugs of abuse. This urine sample will also be used for later analysis of drug levels in your urine. Finally an audiometry test will be performed, as before.

Providing that these results are still acceptable, you will be deemed eligible to receive the study medication on Day 1. You will now be required to stay in the Clinical Centre overnight and for a further 48 hours after administration of the study medication.

You will be required to fast overnight for at least 8 hours before administration of the study medication on the morning of Day 1. Prior to drug administration on the morning of Day 1 you will receive a further physical examination and your blood pressure and pulse will be recorded. You will also be asked to empty your bladder at this point. Prior to administration of the study drug there will be a blood sample taken which will be used for later analysis of the drug levels in your blood. Once these procedures have been performed the study medication will be administered intravenously over a 30-minute period.

Blood samples, for the measurement of drug levels in your blood, will then be taken at the following times: immediately after the infusion is complete (0mins),

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15mins, 30mins, 1, 1.5, 2, 4, 6, 12 and 18 hours post dose. Further blood samples will also be taken on the morning of Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 14, Day 21 and Day 28. You will be required to stay in the Clinical Centre for the first 48 hours. However, following this you may leave the Clinical Centre but will be required to return each morning on Days 4-7 and Day 14, Day 21 and Day 28 for the subsequent blood samples, urine samples, physical examinations and audiometry tests, as detailed below.

Any urine passed over the 48 hours following drug administration will be collected for analysis. Urine collections over this 48 hour period will be at timed intervals of 0-4, 4-8, 8-12, 12-24, 24-36 and 36-48 hours.

Blood pressure and pulse will be recorded throughout the drug infusion and five minutes prior to each blood sample. An ECG will be performed 1 hour after completion of the drug infusion.

In addition to the urine collected over the first 48 hours period, further samples will be required at the following times: the morning of Day 4, Day 5, Day 6, Day 7, Day 14, Day 21 and Day 28. You should not pass urine after rising and before arriving at the Clinical Centre.

An audiometry test will also be performed on Day 2 and Day 7.

You will receive a daily physical examination on Day 1 - Day 7 and blood samples will also be taken at the following times to check your health status: Day 1, Day 4, Day 7, Day 14, Day 21 and Day 28. You may be discontinued from the study without your consent if the investigator feels it would be in your best interests or if you fail to follow instructions from the study staff.

MULTIPLE DOSE STUDY

Study Summary

This part of the study involves the daily administration of BI 397 over a period of seven days. The study medication will be administered intravenously by an investigating doctor. There are six treatment groups, each of which will be made up of 8 subjects per group. The doses of BI 397 administered will start low and progress to the maximum study dose providing that the previous dose was well tolerated. The doses to be assessed are: 70mg, 140mg, 220mg, 360mg, 560mg and 900mg. You will take part in only one of these treatment groups. You will randomly be assigned to receive either the active drug (BI 397) or a placebo which does not contain any active drug. For every three subjects in your group that receive the active drug, one subject will receive the placebo. Neither yourself nor the staff at Simbec will know whether you have been administered the active drug or the placebo.

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Study Procedures

If your pre-study examination is acceptable you will be asked to participate in the study. You will be asked to attend the Clinical Centre on Day -2 for a further audiometry test. Following this, you will be required to attend the Clinical Centre on the day prior to dosing (Day -1). The following procedures will then take place on Day -1: firstly, your medical history will be recorded and a physical examination will take place. An ECG will also be performed and your blood pressure and pulse will be recorded. In addition a blood sample will be taken to check your health status. If you are female this blood sample will also be used to test for pregnancy. You will also be asked to provide a urine sample so that we can check your health status and test for drugs of abuse. This urine sample will also be used for later analysis of drug levels in your urine. Finally an audiometry test will be performed, as before.

Providing that these results are still acceptable, you will be deemed eligible to receive the study medication on Day 1. You will now be required to stay in the Clinical Centre overnight and for a further 7 full days, leaving on the morning of the 8th day.

You will be required to fast overnight for at least 8 hours before each administration of the study medication. Prior to each drug administration you will receive a further physical examination, your blood pressure and pulse will be recorded and a blood sample will be taken. Before administration of the study medication on Day 1, you will also be asked to empty your bladder. The following procedures will then take place on these designated days:

Day 1 & Day 7

On Day 1 and Day 7 the study medication will be administered by intravenous infusion over a 30-minute period. Blood samples will then be obtained at the following times after completion of the infusion: 0mins, 15mins, 30mins, 1, 1.5, 2, 4, 6, 12 and 18 hours post dose. Blood pressure and pulse will be recorded throughout the infusion and five minutes before blood sampling. An ECG will be performed 1 hour after completion of drug infusion on these days.

You must also collect any urine passed over the 24 hour period following drug infusion, at timed intervals of 0-4, 4-8, 8-12 and 12-24 hours.

Blood samples to check your health status will be obtained on Days 1 and 7.

An audiometry test will also be performed on Day 7.

Day 2 - Day 6

On Days 2-6 you will receive further daily intravenous infusions of the study medication. As outlined above, you will be required to provide blood and urine samples prior to drug infusion on Days 2-6. The infusion will take place over a 30-
mins

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minute period. Blood pressure and pulse will be monitored throughout the drug infusion.

You will also be required to provide urine samples prior to drug infusion on Days 2-6.

An audiometry test will be performed on Day 2.

A blood sample to check your health status will take place on Day 4.

Day 8

You may leave the Clinical Centre on Day 8, following a physical examination and after a blood and urine sample have been obtained. However you will be required to return to the Centre for the subsequent blood samples, urine samples, physical examinations and audiometry tests on Days 9-Day 28, as detailed below:

Day 9 - Day 28

Blood samples will be obtained in the mornings on Day 9-14 and on Days 17, 19, 21 and 28. These samples will be used to measure the concentration of drug in your blood and, on certain days, may also be used to check your health status.

An audiometry test will be performed on Day 14, Day 21 and Day 28.

In addition to the 24 hour urine collection on Day 1 and Day 7, you will also be required to provide a urine sample every morning on Day 9-14 and on Days 17, 19, 21 and 28. On these days you should not pass water after rising and before arriving at the Clinical Centre.

In addition to the physical examinations on Day 1 - Day 7, an examination will also be performed before you leave the Clinical Centre on Day 8 and on your final visit on Day 28. You may be discontinued from the study without your consent if the investigator feels it would be in your best interests or if you fail to follow instructions from the study staff.

END OF STUDY ASSESSMENTS

The measurements made on Day 28 (Single and Multi Dose Study) will form your post-study assessment. Provided that all the results from these tests are acceptable you will be discharged from the study. You will, however, be reminded to contact the staff at Simbec should you experience any side effects or illness.

Restrictions

You must not have taken part in a Phase I clinical study at Simbec or elsewhere during the previous 12 weeks.

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Whilst at Simbec you must eat only food provided to you and drink only fluids provided to you. For the first 2 hours following intravenous infusion of the study drug, you will be required to consume 500ml of fluids per hour. After that you may consume fluids freely. However you will be required to consume at least 2 litres and not more than 3 litres of fluid each 24 hour period that you are in the Clinical Centre.

You will have to avoid drinking coffee, tea, drinking-chocolate and other caffeine-containing foods and drinks whilst you are at Simbec. You will fast overnight prior to dosing and for 4 hours after each intravenous administration. After this your meals will be standardized and provided to you according to the clinical schedule.

During fasts only clear fluids will be allowed.

You must not take any drugs or medicine prescribed by a doctor within six weeks of entering the study, or any drugs or medicines bought in a pharmacy within 14 days prior to participation. Throughout the study period you must not take any drugs or medicine, whether prescribed to you by a doctor or bought in a pharmacy without calling Simbec first.

You will only be permitted to smoke in one designated area (the Volunteer Recreation Room) whilst at Simbec.

Alcohol intake must be restricted to two units per day from 7 days prior to the study and alcohol is to be avoided 48 hours before dosing and throughout the whole study.

You must not undertake any exercise more strenuous than normal walking throughout the whole study period.

You must not give a blood donation for at least one month after the study ends.

You will not be permitted to use the Volunteer Recreation Room until 8 hours after each dose. Following this, use of the Volunteer Recreation Room will be at the discretion of the investigator.

Males participating in this study are required to use a barrier method of contraception for a period of 1 month following the final administration of the study drug.

Adverse Effects

Taking part in this study is not expected to be of any medical benefit to you.

Since this is the first time that this drug has been administered to humans, the side-effects you may experience are not yet known, although drugs of the glycopeptide family to which BI 397 is related are known to cause both kidney damage and, rarely, hearing loss.

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A total of approximately 165ml (single dose study) and 250ml (multiple dose study) blood will be withdrawn from you during this study. This is less than that removed during a normal blood donation.

Prior to the study you will have a full medical check including recording of your medical history and you will have blood tests and an ECG to check that you are in good health. These will all be repeated within 3 to 7 days after the end of the study.

We may be required by law to disclose the results of the study and the data generated from the study may be submitted to the Medicines Regulating Bodies of one or several countries. You will not be referred to by name in any of these reports and your medical confidentiality will be respected.

Some insurance companies may view your taking part in a clinical trial as affecting the conditions of any life insurance policies you may have and we recommend that you check with your insurance company - we will give you an explanatory letter for them if you so wish.

The study has been considered by and its conduct approved by an Independent Ethics Committee.

A full protocol explaining all aspects of the study is available within the unit and a member of staff at Simbec will give you access to a copy if you so wish.

This study is undertaken according to the ethical guidelines of the Declaration of Helsinki (South Africa 1996) and complies with the recommendations of the Royal College of Physicians on Healthy Volunteers (1986) and also complies with local laws, recommendations and guidelines at present in force in the United Kingdom for the investigation of new therapeutic agents.

For most studies we need to recruit extra subjects (reserves) in case another subject drops out at the last minute because of illness, problems with tests or other issues. We cannot always say who will be the reserves prior to the study day itself. We cannot guarantee that you will participate in this study and therefore receive full payment.

If we are unable to include you in this study you will receive a payment which will reflect the inconvenience of the study procedures in which you have been involved.

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ISSUE 3: 6 OCTOBER 1999
SIMBEC RESEARCH LIMITED

I have read the above information and been given the opportunity to ask questions.
The information and explanations have been given to my satisfaction and I
understand what is required of me if I participate in this study.

Subject Signature: _____ Date: _____

Investigator Signature: _____ Date: _____

Name of Volunteer: _____
(Please Print)

A Number: A _____


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INFORMED CONSENT FOR HIV ANTIBODY TESTING

STUDY TITLE: A randomized, placebo controlled single and multiple dose, dose-escalation study in healthy volunteers to determine the safety, tolerability and pharmacokinetics of BI 397 given intravenously

PROJECT NO: RD 587/22197


1. **INTRODUCTION:** HIV ANTIBODY TEST is a test currently being used to determine if someone may have been infected by the AIDS VIRUS. The test does not tell if you have AIDS or if you will get AIDS. The significance of a positive or negative test result is unknown at this time since it takes 4 to 6 weeks or longer from exposure to the AIDS virus to positive results in the blood. A positive test result should be confirmed by further testing.

The sponsor of this study requests that this test will be run on all subjects wishing to participate in the study, and Simbec Research is required to perform this test.

2. **PROCEDURE:** If your test result to the AIDS antibody test is negative and all other laboratory test requirements are within the range as required by the protocol, you will qualify for entry into the study. The test results will become part of your case report form.

If your test result to the AIDS antibody test is positive, you will not be allowed to enter the study. Your laboratory results will be given to you or destroyed. Simbec Research will also refer you with your permission to a special clinic which will provide a more specialized test and counselling. This clinic operates on a code which assures your confidentiality. Simbec Research Limited cannot be held responsible for any further testing or treatment.

It must be emphasized that, the mere fact of undergoing this test could adversely affect your ability to obtain life insurance, health insurance, a mortgage, employment and other services.


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SIMBEC RESEARCH LIMITED

You have read and fully understand the information stated above, and you willingly sign this consent form, a copy of which will be given to you. You understand that you have not waived any of your legal rights by signing this document.

VOLUNTEER'S SIGNATURE

DATE

A NUMBER: A

INFORMED WITNESS

DATE


4 Oct 1999