BZ-371 – SUPPORTIVE THERAPY TO MAINTAIN PENILE INTEGRITY IN PROSTATE CANCER PATIENTS SUBMITED TO RADICAL PROSTATECTOMY

BZ371CLI003 STUDY
(NCT05332340)

"Phase 1 Clinical Trial to evaluate safety and pharmacokinetic of BZ371A in a gel form applied in the genitalia of healthy men and women"

INFORMED CONSENT FORM

Study Title: Phase 1 clinical study to evaluate the pharmacokinetics and safety of BZ371A in gel form applied to the genitalia of healthy men and women

Study Code: BZ371CLI003

Sponsor: Biozeus Biopharmaceutical S.A

Principal Investigator: Regina Mayumi Doi

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Please read the following information carefully. Feel free to ask as many questions as you like. The study team will explain to you any words or text that you don't clearly understand.

Introduction

You have been invited to participate in a clinical trial that has received prior approval from an Ethics Committee for Research (ECR). The ECR is an independent organization whose responsibility is to ensure the protection of rights, safety, and well-being of human subjects involved in a study. This clinical trial is a research involving human subjects with a medication derived from the venom of the Brazilian armed spider, called BZ371A, at a concentration of 5 mg/ml. This research, funded by Biozeus Biopharmaceutical S.A., is indicated for patients who have undergone radical prostatectomy surgery (surgery performed on patients with prostate cancer) and subsequently experience inability or difficulty in achieving or maintaining a firm erection sufficient for sexual intercourse. This document, called the Informed Consent Form or simply "ICF," will provide you with very important information about the study, including how it will be conducted (what will happen) and what you will be required to do during your participation. All the information presented here should assist you in making the best decision (whether to participate or not in the study).

In this study, it will be verified whether the medication BZ371A is safe and tolerable when used, meaning it does not cause adverse reactions. Additionally, it aims to assess systemic bioavailability, which means to determine the presence of the peptide (active substance that produces the medication's action), and its fragments, in the blood through the analysis of absorption, distribution, the speed at which the drug is detected in the blood after administration, and the elimination time of the medication from the body.

It is necessary for you to understand the importance, procedures, benefits, risks, discomforts, and precautions of the study, as well as the available treatments for you and your right to withdraw from the study (to quit participating) at any time, regardless of the reason. Please carefully read the information and discuss it with anyone you wish, such as a friend, relative, or your trusted doctor. If you have any questions, seek clarification from the study doctor or the research center professionals involved in the study until you fully understand the information described in this document. Remember, your participation in this study must be voluntary, and you should make your decision only after reading, understanding, and clarifying all your doubts. Your regular medical care will not be affected if you decide to participate, and you will continue to receive any health-related assistance from your doctor.

It is important that you are completely honest with the study doctor about your health condition, including any current or past illnesses, as well as the use of any medications, to ensure your safety during participation in this study. If you have participated in any other clinical trial in the last 12 months, you will not be able to participate in this research.

If you decide not to participate in this study, it will not affect the medical care you already receive for your health. The study doctor will inform you about other available treatments and, if necessary, refer you to the appropriate professional.

After reading and understanding all the aspects of this study and if you agree with everything described here, you will be asked to sign two copies of this document, which will be given to you. In addition, please add an initial in each page (located at the bottom of each page).

What are the study goals?

The goal of this study is to determine whether the drug BZ371A is safe and tolerable when applied topically in the genital region of men and women. In addition, the study aims to determine the systemic presence of the drug, and/or its fragments, in the blood through pharmacokinetic studies, that is, to analyze the absorption, distribution and elimination of the medication in the body after administration.

How many people will participate in the study?

Approximately 12 research participants of both sexes, aged over 18 years and with body mass index (weight-to-height ratio) > 19 and < 28.5 Kg/m2, considered clinically healthy, will be recruited for this study. The study will be conducted in Brazil, being carried out in a single research center.

How long will I stay in the study?

The total period for your participation in the study will be approximately 07 days, however it may vary to more or less. During the study period, you will have 03 visits in which some examinations and evaluations will be carried out.

In related to women: "what if I am pregnant and/or breastfeeding?"

Although the drug has been studied in humans before, studies in pregnant women have not been conducted and it is not known what types of harm it can cause to the baby. Therefore, women of childbearing potential can only participate in the study if they present a negative pregnancy test during the screening/selection period.

You will be considered as capable of becoming pregnant if you are not in menopause (period of definitive cessation of menstruation) or if you have not undergone a hysterectomy (surgical procedure that removes part or all of the uterus) or tubal ligation (definitive sterilization). You will also be considered able to become pregnant even if: you are using a contraceptive method; your sexual partner is using a contraceptive method; if your sexual partner is sterile.

If you are found to be able to become pregnant, you must agree to use a clinically accepted method of contraception for the entire period you remain in the study. The study doctor will evaluate with you what is the best contraceptive method to be used.

How do the drugs in the study work?

The investigational product BZ371A is a topically applied gel (gel widely used in cosmetic products), with only local action, which contain a modified fraction of the original toxin of the venom of the Brazilian wood spider (Phoneutria Nigriventer) and has been shown to maintain an erection of the penis sufficient for a satisfactory sexual intercourse. It has been produced, carefully analyzed and controlled by rigorous processes and is ready to be used in humans. BZ371A acts by increasing blood flow which consequently causes the erection of the penis, allowing a quick onset and at the same time lasting effect.

What will happen to me in this study?

If you decide to participate in this study, you will receive a dose of the BZ371A product. This dose will be applied to verify the safety, tolerability and pharmacokinetics of the drug.

The dose of the drug to be tested in the study is:

- Concentration of 5 mg/ml, applied to the genital region (entire penis, including glans; and clitoris, large and small labia), in a volume of 1.5 ml. The genital region should be washed previously with water and mild soap, followed by drying. The product should be applied with a glove by the trained nursing professional.

Study procedures

Before performing any procedure related to this study, you must demonstrate that you understand and agree to voluntarily participate in the study, thereby providing your rubric at the end of each page of this document, as well as your signature on the last page.

During the study, you must attend the Research Center at 03 different times, being:

I. *Screening (Visit -1 – Day -1): It will occur between 7 to 0 days before the administration of the product.*

On this visit you should be fasting for between 6 to 10 hours, but after the blood collection procedure you will be able to eat without restrictions. Water intake during procedures is free. The procedures you will perform on this visit are described below:

- ✓ *Sign the ICF;*
- ✓ *Assign a unique identification code that should be used in all study documentation, thus maintaining your right to confidentiality;*
- ✓ *Measurement of vital signs, demographic data and recording of data regarding your general health (blood pressure, frequency at which your heart is beating, respiratory rate, your body temperature, weight, height and BMI which is the fat index of your body);*
- ✓ *Clinical evaluation (record of the diseases you have already had or have, medications you have already taken or still take, diseases that have already happened in family members, etc.);*
- ✓ *Complete physical evaluation (general verification of diseases that may be present in the skin and/or other organs and systems of your body such as: muscle, lung, heart, stomach, intestine, kidneys, etc.) and specific evaluation (including examination of the genital organ);*
- ✓ *Blood collection for the following laboratory tests: Blood count (blood), including platelets; coagulogram, including TAP and TTP; biochemistry, including glucose, sodium, potassium, urea, creatinine (renal profile – kidneys), chlorine, total calcium, phosphorus, total proteins and fraction (albumin and globulin), GOT or AST, TGP or ALT, Gamma GT (liver profile), alkaline phosphatase, total cholesterol HDL cholesterol, triglycerides, pH; urine collection (EAS); and β-HCG (for women only);*
- ✓ *Electrocardiogram for cardiac (heart) evaluation;*
- ✓ *Evaluation of concomitant medications;*
- ✓ *Evaluation of the inclusion and exclusion criteria of the study.*

II. *(Visit 0 – Day 0): Product administration.*

In this visit, you will receive breakfast before the start of blood collections and another one 2 hours after the application of the product. You are free to drink water throughout the entire visit. The procedures that will be performed during this visit are described below:

- ✓ *Measurement of vital signs, demographic data and recording of data regarding your general health (blood pressure, frequency at which your heart is beating, respiratory rate and temperature of your body);*
- ✓ *Clinical evaluation (clinical update of your diseases and the medications you take or took between visit V-1 and V0), including examination of the genital organ;*
- ✓ *Evaluation of concomitant medications.*
- ✓ *Evaluation of the inclusion and exclusion criteria of the study;*
- ✓ *Blood collection for pharmacokinetic analysis at the following times: immediately before the application of the product, and 15, 30, 60, 180 and 360 minutes after the application of the product.*
- ✓ *Administration of the drug (you will make use of the product under investigation of the study);*
- ✓ *Blood collection for the following laboratory tests: Blood count (blood), including platelets; coagulogram, including TAP and TTP; biochemistry, including glucose, sodium, potassium, urea, creatinine (renal profile – kidneys), chlorine, total calcium, phosphorus, total proteins and fraction (albumin and globulin), GOT or AST, TGP or ALT, Gamma GT (liver profile), alkaline phosphatase, total cholesterol HDL cholesterol, triglycerides, pH; urine collection (EAS). After application of the product under investigation;*
- ✓ *Electrocardiogram for cardiac evaluation (heart), after the application of the product under investigation;*
- ✓ *Reporting of adverse events (any symptoms or complaints you may have)*
- ✓ *General guidelines for the next visit.*
- ✓ *In this visit you must remain in the center for approximately up to 8 hours;*

III. *Security Review (Visit 1 – Day 7)*

- ✓ *In this visit you will perform the following procedures:*
- ✓ *Complete physical evaluation (general verification of diseases that may be present in the skin and/or other organs and systems of your body such as: muscle, lung, heart, stomach, intestine, kidneys, etc.) and evaluation of the genital organ;*
- ✓ *Measurement of vital signs, demographic data and recording of data regarding your general health (blood pressure, frequency at which your heart is beating, respiratory rate and temperature of your body);*
- ✓ *Evaluation of concomitant medications;*
- ✓ *Electrocardiogram for cardiac (heart) evaluation;*
- ✓ *Reporting of adverse events (any symptoms or complaints you may have)*
- ✓ *General guidelines and exemption from the study.*

Responsibilities of participants

If you decide to participate in the study, you will be responsible for following all instructions and guidelines provided by the study physician as well as the professionals at the Research Center. Such responsibilities include attending all scheduled appointments, performing all procedures and activities related to the study, reporting any change in the medications you use or usually take at home, as well as any change in your health and/or occurrence of any undesirable effect you feel.

What are the risks I will have with this study?

The safety and tolerability of related to the use of the drug(s) are already known from previous animal and human studies. However, like all medicines, undesirable reactions can occur, although some of these are relatively rare (almost not at all). Among the most common reactions we can mention local reactions, such as allergy, irritation or sensitivity, which can manifest as skin *rash*, urticaria and edema; and effects based on the dilation of blood vessels, such as hypotension (low pressure), headache and priapism (painful penile erection).

Other possible risks related to the study procedures are associated with blood collection, such as pain at the site of needle insertion, the appearance of hematoma (purplish spot on the skin as from a "blow") and phlebitis (thicker blood) and the performance of electrocardiogram, such as the appearance of skin irritation in the places where the electrodes will be placed. In addition, you will be fasting for blood collections at V-1.

In case you experience any of the above unwanted reactions, as well as other reactions besides these, during the study, the Research Center team as well as a doctor will be available to perform all the necessary procedures for the full resolution of the clinical conditions.

Will I get benefits from this study?

This is a phase 1 study for safety evaluation in healthy people, so no individual benefits are expected to occur. This study could benefit several patients in the future if this proposed intervention proves to be safe and effective.

What is the cost of participating in this study?

You will have no costs to participate in this study. Medical care, study medications, tests, and procedures will be provided at no cost to you by the study sponsor.

Study medications will be provided to you at no cost during the study.

The sponsor of this study will also bear the expenses related to all examinations required by the study.

Therefore, your participation in this study will not generate any expenses for you.

You will also be guaranteed, without costs, in case any adverse event (complaints or problems) appears during the study course. In this case, all procedures, examinations, consultations, and medications necessary for the resolution of the clinical condition will be paid by the sponsor.

Will I be paid for participation in this study?

You will not have any financial gain or loss by participating in this study. All your accommodation expenses, when required, transportation and food for each day of visit, or extra study visits, and in case of emergency to treat possible adverse events, will be fully covered by the study sponsor.

If a companion is required during visits or in emergency cases, this person's expenses will also be covered by the study sponsor.

Compensation and/or medical treatment in case of damages arising from the research

You, the SUS or medical plan will not pay for any medication, examination, procedure or test requested as part of this study. All such costs will be fully covered by the Study Sponsor.

In cases of direct or indirect, immediate or non-immediate, damage resulting from your participation in the study, you will also receive, as part of the immediate, complete and comprehensive assistance, the medications, procedures and examinations necessary for the control of your health condition (such as to treat adverse events) that are necessary.

The follow-up and/or treatment of direct or indirect, immediate or late, damages suffered in the course of participation in the study will be the responsibility of the study physician and the Sponsor. If this happens, you will be medically followed up (with all costs paid by the Sponsor) by the Research Center for as long as necessary, even if the relationship between the damages and the study drugs is not established.

In this way, in case of any injury, damage or disability in any way arising from your participation in the study, you will receive full and immediate assistance, free of charge for as long as it is necessary. The costs of these medical and non-medical expenses will be the responsibility of BIOZEUS Biopharmaceutical S.A.

By signing this consent form, you are not waiving any legal rights, including the right to seek compensation for damages resulting from your participation in this study.

Confidentiality

The guarantee of confidentiality and privacy of your data will be ensured in accordance with Brazilian regulations. All information obtained during this study, including your medical records, personal and research data are confidential.

The sponsor, its representatives and the study team will take all necessary measures to ensure the confidentiality and privacy of your data involved in the research. The way to ensure this confidentiality will be to identify you through an alphanumeric code that only the study team will be able to relate to you.

In relation to your medical examinations carried out during the study, you will have the right to know the results of these and, if it is of interest to you, a copy of them may be provided to you.

During your participation in this study, your doctor will collect your personal data as well as data about your health, which will always be passed on to the study sponsor in coded and anonymous form. You have the right to access your data with the study physician and ask for corrections if they are wrong or incomplete. The

sponsor will statistically analyze the data to determine the results of the study. In addition, its coded and anonymous data may be used in scientific publications in the future.

This information will be kept by the investigator and the sponsor and will not be used for any other purpose during this period. If you have a customary personal physician, and only if you agree, the study physician will inform your personal physician about your participation in the study.

Withdrawal and/or discontinuation of the study

The decision to participate in this study is yours alone. If you do not want to participate, or decide to withdraw your consent at any time, you will not suffer any kind of punishment or loss of the benefits to which you are entitled, nor will you need to provide any information regarding your withdrawal.

It is important that you do not participate in the study against your will. If you want to give up, you can let us know as you like, either by phone, email or even in person.

Your participation in this study may be discontinued at any time by the physician in the following cases:

- If the continuation in the study does not meet your interest and if it is potentially dangerous to your well-being or health;
- If you do not adhere to the study procedures and instructions as directed by the doctor or study team.

The study may also be discontinued at any time by the Sponsor, the Brazilian Sanitary Authority (ANVISA/Ministry of Health), the Research Ethics Committee (CEP) and/or the National Research Ethics Committee (CONEP), after analysis of the reasons for the discontinuity by the Research Ethics Committee that approved it. However, this interruption will not in any way impair the medical follow-up to which you are entitled.

In the event that termination of your participation in the study becomes necessary by the Investigator or you decide to terminate your participation before the scheduled date (before the final visit - VF), you should inform all the professionals involved in the Research Center as soon as possible, so that they can ensure that the appropriate study procedures are followed and that a final evaluation visit is carried out to determine whether the treatment you have performed did not harm his health.

New information available

You will be informed by the study physician of any new relevant information that becomes available in the course of this research that may affect the decision as to your participation as soon as possible. He will discuss with you about whether or not you want to continue the study.

Contacts

To clarify doubts related to this research, to report an injury related to your participation in the research or to obtain information about the procedures of the study, you can contact, during any stage of the study,

the professionals responsible for the research. You also have the right to be kept up to date on the partial results of the study (when defined this partial analysis in protocol), which are known to the researchers, if it is of interest to you.

If in doubt, you can contact the study doctor Dr. (a). Regina Mayumi Doi, at any time at the address and telephone numbers provided below.

Institution: Azidus Brasil Pesquisa Científica e Desenvolvimento Ltda.
Address: Rua General Osório, nº 507, Vila Martina – Valinhos (SP)
Phone: (19) 3829-6160 (office hours)z

In case of emergency, you can contact the study doctor through the following phone (24 hours):
Dr. Regina Mayumi Doi
Phone: +55 (19) 98157-0880

If you have any considerations, doubts and/or questions about your rights as a participant in this study, or if you are not satisfied with the way the study is being conducted, you can contact the Research Ethics Committee (CEP) of the Faculty of Medicine of Jundiaí, which is responsible for the analysis and approval of this project, the monitoring the ethical aspects of all research involving human beings, aiming to ensure the dignity, rights, safety and well-being of the research participant.

The Research Ethics Committee Faculdade de Medicina de Jundiaí can be contacted at Rua Francisco Telles, 250, Vila Arens – Cidade de Jundiaí or by phone (11) 3395-2120. Calling hours are Monday through Friday from 8:30 a.m. to 11:30 a.m. and from 2:00 p.m. to 5:00 p.m.

Assent

I believe I have been sufficiently informed about the information I have read or that has been read to me, describing the study "Phase 1 clinical study to evaluate the pharmacokinetics and safety of BZ371A in gel form applied to the genitalia of healthy men and women"

I discussed with the study physician about my decision to participate in the research. The purposes of the study, the procedures to be carried out, its discomforts and risks, the guarantees of confidentiality and permanent clarifications became clear to me. It was also clear that my participation is free of expense and that I am guaranteed access to hospital treatment when necessary. I voluntarily agree to participate in this study and may withdraw my consent at any time, before or during it, without penalty or prejudice in my care in this service, without loss of any benefit I may have acquired. I confirm that I have added my initials, signed and dated this consent document and that a copy of it has been given to me.

Research Participant:

Name	Signature	Date of Signature

Legally acceptable representative (if applicable):

Name	Signature	Date of Signature

Witness (if applicable):

Name	Signature	Date of Signature

Responsible for the application of the ICF:

Name	Signature	Date of Signature