Participant Information and Consent Form
Version 3 dated 30th September 2010

Study Title: An open-label, phase 2, single centre, randomised, crossover design bioequivalence study of AndroForte® 5 Compared With Testogel® 1% in Hypogonadal Men

Sponsor: Lawley Pharmaceuticals

Protocol Number: LP 101

Site: Pain and Anaesthesia Research Clinic – Royal Adelaide Hospital

Principal Investigator: Professor Gary Wittert

You are invited to take part in this research project. This Participant Information and Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research. Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

This is a research project and you do not have to be involved. If you do not wish to participate, your medical care will not be affected in any way. Also, you may withdraw from the project at any time after you have commenced.

If you do decide to participate, you will be given a signed and dated copy of this participant information sheet and consent form for your records.

Introduction

You have been asked to participate in this study because you have low testosterone levels and are either currently receiving testosterone replacement therapy or meet the criteria for starting testosterone replacement therapy but have not yet commenced treatment.

Recent studies have shown that applying a testosterone-containing gel to the skin (transdermal) is an effective way to increase testosterone levels. In Australia Testogel® 1% is registered and approved by the Therapeutic Goods Administration (TGA) for this use. Testogel® 1% is also approved for this use in many other countries outside Australia.

More recently an Australian company (Lawley Pharmaceuticals) has developed a testosterone cream (AndroForte® 5), which was shown to have reasonable efficacy, safety and acceptability over a three-month period in a previous study. This aim of this research study is to determine if a testosterone cream (AndroForte® 5) is as effective as the testosterone gel (Testogel® 1%) in increasing testosterone levels in the body. AndroForte® 5 is registered for use in Western Australia and for export internationally, however as it not licensed for use throughout Australia, it is referred to as the "experimental treatment".

What is the purpose of this research?

The purpose of this research study is to;

- Determine if AndroForte® 5 produces the same increase in blood testosterone as Testogel® 1%
- Determine the safety of AndroForte® 5 compared with Testogel® 1%. This will include looking at what side effects occur and how often they occur.

How many people will take part in this study?

We expect that approximately 16 participants will take part in this study.

What is involved in the research study?

During this study you will receive both, AndroForte® 5 and Testogel® 1%. Either AndroForte® 5 for 30 days and then, after a small break, Testogel® 1% for 30 days or vice versa. This is known as a cross over design.

If you decide to participate and you match the study criteria, the sequence in which you receive each study treatment will be determined by chance (like tossing a coin) so you have an equal chance of receiving either:

AndroForte® 5 followed by Testogel® 1% **or** Testogel® 1% followed by AndroForte® 5.

You and the study team will know the treatments you are receiving.

You will receive the first treatment (Treatment Period I) for 30 days. You will then cease the treatment and have a small break ("the washout period") which will last for 7-10 days. After the washout period you will commence the second treatment (Treatment Period II). Following 30 days of the second treatment you will cease the treatment and attend an End of Study visit.

Throughout the study you will be required to have a total of 8 clinic visits which includes 4 overnight stays in hospital. All of these visits will take place at the Pain and Anaesthesia Research Clinic (PARC) at the Royal Adelaide Hospital. You will need to stay overnight on Day 1 & Day 30 during each treatment period (Treatment Periods I and II). In addition you will need to attend the clinic on Day 15 of each treatment period. You will be contacted by phone each week by the study staff to check on your progress.

At pre-determined points during each treatment, blood samples will be taken to measure the levels of testosterone and other hormones in your blood.

What are the study treatments and how will they be used?

AndroForte® 5: is a cream that is applied from the tube using an applicator. The research staff at the clinic will apply the first dose during your first overnight stay. After that you will be required to apply 2 ml (equivalent to 100mg) of the cream to clean, dry and intact skin on the torso every day for the remainder of the treatment period. Your final dose will be applied while you are in the clinic on Day 30 for your second overnight stay. The cream should be applied at approximately 9.00am each day and it should be massaged into the skin for approximately 60 seconds until all the cream is absorbed. After application, thoroughly wash hands with soap & water to avoid secondary exposure.

Testogel® 1%: The gel is supplied in a sachet. The research staff at the clinic will apply the first dose during your first overnight stay. You will be required to apply the entire contents of a single sachet (equivalent to 50mg) to clean, dry and intact skin on the torso every day for the remainder of the treatment period. Your final dose will be applied while you are in the clinic on Day 30 for your second overnight stay in this treatment period. The gel should be applied at approximately 9.00am each day and the area should be left to dry for a few minutes before dressing. After application, thoroughly wash hands with soap & water to avoid secondary exposure.

Following the application of the cream or gel you must not shower or wash the area (or go swimming) for 6 hours. You may shower either prior to application of the treatment in the morning, or before bed in the evening.

During the study if you forget to apply a morning dose prior to 9:00 AM it can be applied later in the day provided it is within 9 hours of the usual time of application. If it is after 9 hours, the dose should not be applied and record this missed dose in your Diary Card.

Pharmacokinetic Samples (PK Samples)

Pharmacokinetic samples (PK) are blood samples that are taken to measure the level of testosterone and other hormones in your blood and will be collected from a cannula (a small plastic tube) placed into a vein in your arm. On Day 1 and Day 30 of each treatment period you will need to have an overnight stay at PARC for PK sample collections. At each stay, blood samples will be collected at the following times over a 24-hour period (14 samples - approximately 64 mls of blood in total):

- 15 and 5 minutes before the first dose and again immediately before the dose
- At 2, 4, 5, 6, 7, 8, 9, 10, 12, 16 and 24 hours after application of study treatment

On Day 15 of each treatment period you will need to have one PK blood sample collected. This sample needs be taken before you apply your morning dose of study treatment. You do not need to fast or adhere to any special requirements prior to this sample being taken. Approximately 4mls of blood will be collected.

Are there any specific restrictions or requirements?

For the PK sampling on Day 1 and Day 30 you must agree to adhere to the following dietary and exercise requirements for 24 hours before each overnight stay:

No caffeine, alcohol or chocolate consumption.

No vigorous physical activity.

You will be required to fast from all food and drink except water for 8 hours before admission (from approximately 11PM the night before admission).

Approximately one hour after the study treatment has been applied you will be provided with breakfast, followed by other meals throughout the day. All of your meals during your period of hospitalization will be provided. You should tell the study staff if you have any specific dietary needs or restrictions.

How long will the study last?

You will be in this research study for approximately 80 - 90 days. This includes the screening period, the two treatment periods and the "wash out" period between treatments.

What does participation in this research involve?

If you decide to take part in this study you will be asked to remain in the study until you have completed the two treatment periods, unless you are unable to tolerate the study treatment, you decide to withdraw consent or the study doctor deems it in your best interest for you to be withdrawn. You will be asked to attend all study visits as outlined in this document and to apply the study treatment every day as instructed by study staff.

You must keep the cream /gel you take home in a safe place and at room temperature. You will need to complete your study diary as instructed by the staff and to return it along with your study medication to each clinic visit. You must tell the research staff about any missed doses and the reason why the dose was missed.

You should not eat grapefruit or drink grapefruit juice during this study and you should report any new medications (including prescription drugs, over the counter medications and herbal remedies) to the study staff *before* you begin using them, for the entire study duration. You will be required to report any illness or change in your health status or potential side effects to the study staff as soon as possible

You will be asked to adhere to the study restrictions as outlined on page 3 of this document. You will be asked to complete a number of questionnaires at various times throughout the study which seek information about your personal and sexual life. You should complete these as accurately as possible and complete all required questions.

If you have a female partner of child-bearing potential you must use appropriate birth control (e.g. condoms) for the entire study duration. To obtain information about how to avoid your partner becoming pregnant, ask your study doctor or nurse. If your partner becomes pregnant while you are taking part in this study you must notify your study doctor immediately.

Visit requirements

Screening visit:

Following confirmation of your willingness to participate in this study, your study doctor must then determine if you match the criteria for enrolment. This will be assessed at a screening visit which will take place up to 28 days before treatment begins.

If you are currently receiving testosterone replacement therapy you will need to stop your testosterone treatment prior to entering the study. The exact length of time you need to stop prior to entering the study will depend on your current treatment. Your doctor will discuss this with you.

The following information will be collected and procedures will be performed at the screening visit:

- Medical history - you will be asked questions about any health problems including past illnesses, surgeries and skin disorders. It is in your best interest to disclose (to best of your knowledge) your full medical history to the study doctor.
- Details of all medicines currently being used or used within the last 4 weeks including prescription and over the counter medicines, creams and lotions, vitamins/dietary supplements.
- Physical examination - including height and weight, waist measurement, blood pressure, pulse rate, breathing rate and temperature.
- Blood tests –approximately 10 ml of blood (i.e. about 3 teaspoons) will be collected for blood tests to assess your general well being. You must not eat or drink (except water) for 8 hours before the blood tests are taken. When you are fasting you should continue taking your usual medicines at the scheduled times unless your study doctor specifies otherwise.
- Urine test - a sample of urine will be collected for routine testing
- Your heartbeat will be examined by an electrocardiogram (ECG)
- Urine drug screen – a test to detect the presence or absence of non prescribed drugs of abuse
- Completion of a questionnaire to assess if you are at risk of prolonged pauses in your breathing when you sleep (sleep apnoea).
- Completion of a questionnaire to assess any difficulties associated with passing urine.

It is possible that after the screening tests and information are reviewed you will not be able to take part in this study. Your study doctor will discuss this with you. If you match the criteria for enrolment into this study, you will be asked to return to the clinic to receive your study treatment. You will be required to attend the clinic for a total of 8 visits - including 4 overnight stays.

Treatment visits:

48 hours prior to Day 1 and Day 30 of each Treatment Period, research staff will phone you to confirm your admission time and to remind you of the following study restrictions:

No caffeine, chocolate or alcohol consumption in the 24 hours prior to commencing treatment

No vigorous physical activity in the 24 hours prior to treatment

Fasting requirements (8 hours prior to clinic visit on Day 1 and Day 30)

Day 1 and Day 30 of each Treatment Period

You will be admitted to the Pain and Anaesthesia Research Clinic at around 7.30am for the following:

- Physical exam and vital signs (blood pressure, pulse, respiratory rate, temperature)
- Completion of Quality of Life Questionnaires
- Review of any change in health or any changes to your medications since your screening visit
- Administration of study drug by the research staff
- Blood sampling for haematology and biochemistry (to assess your general well being) and hormonal assays (approximately 20 mls or 1 tbsp)
- PK samples - 14 blood samples will be collected over 24 hours (approximately 64 mls or 3 tbsp) at the following time points:
- pre dose, at 15 minutes, 5 minutes and just before dosing and after dosing at 2, 4, 5, 6, 7, 8, 9, 10, 12, 16 and 24 hours after application of study treatment

Day 2 of each Treatment Period

Before your discharge home you will:

- Receive education about the study drug and be given a study drug information leaflet
- Receive your study drug supplies and the research staff will observe you applying the drug
- Be provided with a patient diary and given instruction on how the diary is to be completed
- Have your temperature, pulse, respiratory rate and blood pressure taken
- Be discharged and given an appointment to return for your next appointment

Day 7 and 21 of each Treatment Period

The research staff will contact you by phone to:

- Ask about any side effects you have experienced
- Other medications you are taking

Day 15 of each Treatment Period

You will attend the clinic before you apply your morning dose. At this visit the following will be performed

- Blood tests - PK sample, haematology and hormonal tests
- Temperature, respiratory rate, pulse and blood pressure
- An examination of your abdomen
- Review of any side effects, changes in your health status or any changes to your medications

Washout period

During the 7 day washout period (between treatment periods I and II) you will not receive any treatment**.**

End of Study Visit

This visit will be scheduled between 7-14 days after your last dose of study drug in treatment period II **or** if you withdraw or are withdrawn from the study early for any reason. At this visit the following procedures will be performed:

- Physical examination including skin assessment
- Vital signs
- Review of side effects and concomitant medications
- Completion of Quality of Life questionnaires
- Blood test - haematology, biochemistry (to assess your general well being) and hormonal assays
- Urinalysis
- Completion of questionnaire to assess if you have any difficulties passing urine

At this visit your doctor will discuss your condition with you and recommend the appropriate treatment (this may involve recommencing treatment with your testosterone treatment of choice). If you were not receiving testosterone replacement therapy prior to entering the study you may be referred back to your medical practitioner.

Payments

You will be paid $2000 for completing this study. This is to reimburse you for the time involved in attending all the required study visits. Your travel costs will also be re-imbursed.. There will be no out of pocket expense to you for participating in this study. If you are withdrawn from the study by the study doctor due to illness or other reasons you will receive a prorata amount for your participation in the study to the time of your withdrawal. The study drugs will be provided to you free of a charge for the duration of the study. Lawley Pharmaceuticals will pay the study doctor and the Pain and Anaesthesia Research Clinic to conduct this study.

What are the possible benefits?

Participation in this study may not provide you with any benefit. It is possible that your testosterone levels will remain the same, or high but it is also possible that you may develop symptoms associated with low testosterone levels during periods of the study.

What are the possible risks ?

The most common side effects experienced in 10% of subjects treated with Testogel® 1% and AndroForte® 5 are:

- Skin reactions at the application site - e.g. irritation, redness, dry or stinging skin
- Acne

Less common side effects, occurring between 1-10% of subjects treated with Testogel® 1% and AndroForte® 5 include:

- Headaches, dizziness
- Nausea
- Retention of salt and water
- Loss of head hair
- Increased body hair
- Changes in your mood
- Deepening of the voice

The following less common side effects have been reported in 1-10 % of subjects with use of Testogel® 1% **only** : (AndroForte® 5 has not been associated with these side effects, however as it contains testosterone there is a potential for these side effects to occur).

- 'Pins and needles'
- Increased blood pressure
- Painful, tender or enlarged breasts
- Diarrhoea
- Increase in the production of red blood cells
- Increased lipids in the blood

The following less common side effects have been observed during treatment with oral or injectable testosterone in 1-10% of subjects . These potentially may also occur with either Testogel® 1% or AndroForte® 5:

- Difficulty passing urine
- Weight gain
- Changes in liver function tests
- Jaundice (yellowing of the skin)
- Unwanted increased sex drive
- Depression/nervousness/irritability
- Muscular pain
- Oligospermia (reduction in the number of sperm)
- Unwanted priapism (frequent or prolonged and painful erections)

There may be side effects that the researchers do not expect or do not know about yet. Please tell your doctor immediately about any new or unusual symptoms that you experience.

Secondary Exposure

Research has shown that there is the potential for secondary exposure to testosterone by women and children when the testosterone cream or gel is applied to the skin and they come in direct contact with the treated area.

Specific precautions must be followed to minimize the potential for secondary exposure:

- Apply the product as directed
- Wash hands with soap and water after application.
- Cover the application site(s) with clothing (e.g. a shirt) after the gel/cream has dried.
- Prior to any situation in which skin-to-skin contact with the application site is anticipated the application site(s) should be thoroughly washed with soap and water to remove any testosterone residue.
- In the event that unwashed or unclothed skin to which the gel / cream has been applied comes in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible.

Signs of secondary exposure (abnormal development of male sexual characteristics) should be brought to the attention of your doctor immediately. Signs and symptoms to watch for include:

- Women – changes in hair distribution, increase in acne
- Children – unexpected sexual development and aggressive behaviour

Risks associated with the screening and washout period

You may experience some of the symptoms associated with low testosterone levels briefly during the"screening " and "wash-out" periods, which may include lack of energy, erectile dysfunction, decreased sex drive, memory loss and depressed mood. If this occurs you should contact your study doctor.

Risks associated with study procedures

Blood sampling and the insertion of cannula's for blood sampling is associated with some general discomfort. There is also a slight risk of fainting, bruising, swelling or a rare risk of developing an infection or thrombosis (blood clot) at the site of the needle puncture or cannula insertion. There is a slight risk of local skin irritation from the placement of the ECG dots.

What if new information arises during this research project?

During the study new information about the risks and benefits may become evident. Your doctor will discuss the implications (if any) with you at that time and give you the opportunity to review your participation in the study.

Can I have other treatment during this research project?

While you are participating in this study you may not be able to take some or all of the medications that you have been taking. Your doctor will discuss this with you. It is important to tell your doctor and the research staff about any medications you may be taking, including over-the-counter medications, vitamins or herbal remedies as these may have an effect on the study drugs. You should also tell your doctor about any changes to these during your participation in the research.

Do I have to take part in this research project?

Your participation in this study is entirely voluntary. If you do not wish to take part you don't have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any time.

What are my options if I do not want to take part in this study?

The alternative is not to take part in this study. You do not have to participate in this study to treat your condition. Your physician will determine your treatment whether or not you choose to be part of this study.

What if I withdraw from this project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. Your choice to withdraw from the study will not affect your medical care. It will not harm your relationship with your doctor.

Could this research project be stopped unexpectedly?

This study may be stopped due to:

a) Unacceptable side effects

b) A commercial decision by the sponsor (Lawley Pharmaceuticals)

c) A decision by local regulatory / health authorities

What will happen when my participation in this research project ends?

At the completion of the study your doctor will discuss your condition with you and recommend the appropriate treatment (this may involve recommencing treatment with your testosterone treatment of choice). If you were not receiving testosterone replacement therapy prior to entering the study you may be referred back to your medical practitioner.

How will I be informed of the results of this research project?

Data describing the outcome of the study will be available to participants on the Australian and New Zealand Clinical Trial Register website, in press releases and in research articles published in peer reviewed journals.

What else do I need to know?

What will happen to information about me?

This study will involve the collection and processing by your study doctor and study staff of personal information about you and your medical condition - both generally and in connection with your participation in this study. Any information obtained in connection with this research project that can identify you will remain confidential and will only be used for the purpose of this research project.

Information about you may be obtained from your health records held at this and other health services for the purposes of this research. Your health records and any information obtained during the study are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the sponsor, this organisation or as required by law. The relevant authorities include regulatory agencies such as the Australian Therapeutic Goods Administration (TGA) and US Food and Drug Administration (FDA).

Blood samples for pharmacokinetics (PK) will be coded with your subject number and the study number. Your name and other personal information such as date of birth or initials will not be used on any form or blood sample.

The samples will be transferred to a central laboratory. The samples cannot be used for any purpose other than that initially planned and for which you have given consent. At the end of the analysis all samples will be destroyed. If you withdraw your consent from this study, your coded stored PK samples will continue to be used for study purposes unless you request that these samples be destroyed. However any analyses on your samples that have already been performed prior to your withdrawal of consent will continue to be used as part of the overall research. Any data that has already been generated will be included in the final study report and will be kept by the study sponsor (Lawley Pharmaceuticals).

By signing the consent section of this document you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above. Your family doctor may be advised of your participation in this research project.

Study data will be stored securely and will be accessed only by personnel directly involved in the study. All trial-related documents will be kept for a minimum of 15 years after the completion of the study.

In any publication and/or presentation, information will be provided in such a way that you cannot be identified.

By taking part in this research project you agree that samples of your blood and data generated from analysis of these materials may be provided to Lawley Pharmaceuticals. Lawley Pharmaceuticals may directly or indirectly benefit financially from your samples or from knowledge acquired through analysis of your samples.

How can I access my information?

In accordance with relevant Australian privacy and other relevant laws, you have the right to access the information collected and stored about you. You also have the right to request that any information with which you disagree be corrected. Please contact your doctor if you would like to access your information.

What happens if I am injured as a result of participating in this research project?

In the event of injury as a result of participation in the trial, the Sponsor will follow the compensation guidelines proposed by Medicines Australia. You can obtain a copy of these guidelines from your study doctor or alternatively you may view these guidelines at the Association's website http://www.medicinesaustralia.com.au/public/formind.pdf. The provision of compensation under this scheme does not compromise your rights to seek compensation under common law. You should notify your study doctor as quickly as possible of any physical injury or illness.

Is this research project approved?

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research* (2007) produced by the National Health and Medical Research Council of Australia. The Royal Adelaide Hospital Research Ethics Committee has approved this research project.

If you wish to speak to someone not directly involved in the study about your rights as a volunteer, or about the conduct of the study, you may also contact the Chairman, Research Ethics Committee, Royal Adelaide Hospital on 8222 4139 . You should quote the name of the study doctor at the time of your call,

If you have any questions, problems arising from, or injuries related to the study, please contact:

Professor Gary Wittert: Telephone No. 0409 411 789

Melanie Gentgall – PARC Clinical Research Manager: Telephone No. 0403 310 378

ROYAL ADELAIDE HOSPITAL

CONSENT FORM

Version 3, dated 30th September 2010

Study Title: An open-label, phase 2, single centre, randomised, crossover design bioequivalence study of AndroForte® 5 Compared With Testogel® 1% in Hypogonadal Men

Principal Investigator: Professor Gary Wittert

1. The nature and purpose of the research project has been explained to me. I understand it and agree to take part.
2. I understand that I may not benefit from taking part in the trial.
3. I understand that, while information gained during the study may be published, I will not be identified and my personal results will remain confidential.
4. I understand that I can withdraw from the study at any stage and that this will not affect my medical care, now or in the future.
5. I understand the statement concerning payment to me for taking part in this study as contained in the Information Sheet.
6. I have had the opportunity to discuss taking part in this investigation with a family member or friend.
7. I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information concerning my health (and the treatment required for this project) to members of the research team. I understand that such information will remain confidential.
8. I agree to have PK blood samples taken and understand these blood samples will be sent to the laboratory in coded form

Name of Participant: _____

Signed: _____ Dated:_____

I certify that I have explained the study to the participant and consider that he understands what is involved.

Signed:_____ Dated:_____

(Investigator)