A randomized, cross-over controlled study to compare the pharmacokinetic profiles of sublingual administered testosterone solution followed by a sildenafil citrate tablet, versus sublingual testosterone and sildenafil citrate combined in one tablet in healthy premenopausal women

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Primary objective:To compare the pharmacokinetics of testosterone and sildenafil citrate following administration of a sublingual solution of testosterone with an encapsulated tablet versus a combination product.Secondary objective:To investigate...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Sexual dysfunctions, disturbances and gender identity disorders
Study type	Interventional

Summary

ID

NL-OMON36050

Source
ToetsingOnline

Brief title
PK - Lybrido Formulations 1 and 2

Condition

- Sexual dysfunctions, disturbances and gender identity disorders

Synonym
problems with sexual functioning, Sexual dysfunction

Research involving
Human

Sponsors and support

Primary sponsor: Emotional Brain BV
Source(s) of monetary or material Support: Emotional Brain BV

Intervention

Keyword: Combination tablet, Sildenafil, Testosterone

Outcome measures

Primary outcome

• Cmax of total testosterone (F2 >= 75% of Cmax F1);

• Cmax of free testosterone (F2 >= 75% of Cmax F1);

• Cmax of sildenafil (F2 >= 75% of Cmax F1);

• AUC0-infinity of total testosterone (F2 >= 75% of AUC0-infinity F1);

• AUC0-infinity of free testosterone (F2 >= 75% of AUC0-infinity F1);

• AUC0-infinity of sildenafil (F2 >= 75% of AUC0-infinity F1);

Secondary outcome

• To investigate the time frame in which the testosterone coating of the

combination tablet is dissolved sublingually.

Study description

Background summary

Lybrido (0.5 mg testosterone + 50 mg sildenafil) is under development by

Emotional Brain BV as an on-demand treatment for (the subset) of women with hypoactive sexual desire disorder (HSDD) characterized by low attention to sexual cues. Hence, Lybrido is intended for use on a per need (i.e., not continuous) basis before proposed sexual activity. The cause of low attention to sexual cues is not well elucidated, but both physiological and psychological factors are believed to be involved. Thus a combined treatment targeting central (testosterone) as well as peripheral/local factors (sildenafil) has been shown to be associated with significant increases in genital arousal, as well as the frequency and quality of sexual encounters (Van der Made et al. 2009a and Tuiten et al., 2011 in preparation).

In the penis, NO released from nerves and endothelium, induces production of cyclic guanosine monophosphate (cGMP); cGMP plays a key role in relaxing smooth muscle, necessary for the induction of an erection. This nucleotide is hydrolyzed by phosphodiesterases, of which PDE 5 exerts the main activity in the corpora cavernosa. Therefore, PDE 5 inhibitors will, during sexual stimulation, enhance the action of NO/cGMP on erectile function (Klotz et al 2001). The genitals of both sexes have common embryological origins. The clitoris consists of an erectile tissue complex, which embeds the anterior vaginal wall. Clitoral erection and the anterior wall of the vagina are highly involved in female sexual arousal and response. This leads to the hypothesis that PDE-5 inhibitors could be effective in women with FSD, but the studies investigating this hypothesis have failed to show comparable efficacy as in men.

Sublingually administered testosterone (0.5mg) has been shown to have a delay in effect of about 4 hours on subjective and peripheral sexual arousal (Tuiten et al, 2000 & 2002) in sexually functional women, but not in women with HSDD (Van der Made 2009a & 2009b). If this central effect of testosterone administration is coupled with enhancement of the peripheral sexual response through the use of a PDE-5 inhibitor, an increase in subjective and peripheral sexual arousal may be observed in women with HSDD. However, the peak effect of the PDE-5 inhibitor must coincide with the peak effect of the 4 hour delay effect of testosterone, So for the PDE-5 inhibitor sildenafil (Tmax approx. 30-120 minutes), one would have to administer the sublingual testosterone first, and after 2-3 hours the sildenafil.

In the first proof of concept study, 0.5 mg testosterone combined with 10 mg vardenafil (which is comparable to 50 mg sildenafil) was compared to 0.5 mg testosterone alone, 10 mg vardenafil alone and a placebo employing a double blind, randomized cross-over design in 13 women with HSDD. Peripheral sexual arousal was measured with the vaginal pulse amplitude (VPA) in response to erotic film excerpts. In a subset of women with low preconscious attentional bias for erotic cues, the VPA increased significantly in the condition of 0.5 mg testosterone combined with 10 mg vardenafil, as compared to the other 3 drug conditions. Neither 0.5 mg testosterone alone, nor 10 mg vardenafil alone showed significant increase as compared to placebo (Van der Made et al.,

2009a). This finding was replicated in a second double blind, randomized placebo-controlled cross-over study with 28 women with HSDD, of which 17 showed low preconscious attentional bias for erotic cues. In this study, the participants also reported an increase in subjective sexual arousal following the viewing of erotic film clips in the condition of 0.5 mg testosterone combined with 10 mg vardenafil, as compared to these substances separately and placebo (Van der Made et al., 2009b). The combination of 0.5 mg testosterone with 50 mg sildenafil was investigated in a double blind, randomized placebo-controlled cross-over study where 57 women with HSDD could use the study medication on demand at home during a period of 4 weeks (4 weeks for Lybrido and 4 weeks for placebo). After each sexual encounter the participants filled in a short sexual event questionnaire in which various aspects of sexual functioning were inventoried. The subjective and physiological sexual response in response to erotic film clips was also measured at the participants* homes using an ambulatory laboratory (see Bloemers et al., 2010). As expected, Lybrido increased subjective and physiological sexual responding at home in the subset of women with low preconscious attentional bias for erotic cues (n=30). More importantly, these women reported more and better sexual activity (i.e. more genital arousal and sexual desire) during the 4-week period of on-demand Lybrido use, as compared to the 4-week placebo period (manuscript in preparation).

In the above reviewed clinical studies, 0.5 mg testosterone was administered sublingually as a solution, followed 2.5 hours later (thus creating overlapping peaks in effect of testosterone and sildenafil) by a 50 mg sildenafil citrate tablet (or 10 mg vardenafil). Because compliance to this method of administration requires accurate and thorough instructions, Emotional Brain has recently developed a combination tablet that will deliver testosterone (0.5 mg) sublingually and, 2.5 hours later, 50 mg sildenafil citrate This will allow women with HSDD to take just one single preparation 3-6 hours before anticipated sexual activity.
This new developed drug product is a mint flavored white tablet of 9 mm in diameter intended for sublingual administration followed by swallowing; after 90 seconds, when the testosterone and mint flavor coating is dissolved. The quickly dissolving outer coating will deliver testosterone (0.5 mg) sublingually, and the time-delayed release core will deliver sildenafil citrate (50 mg) 2.5 hours later. The outer coating comprises testosterone and a mint flavor, so when the mint flavor is gone (estimated to be around 30 sec), the testosterone is fully dissolved and maximally available for absorption via the mucosal membranes.

The present study is part of the ongoing drug development program for Lybrido. This research proposal describes a pharmacokinetic study of which the main goal is to compare the pharmacokinetics of testosterone and sildenafil citrate following administration of a sublingual solution of testosterone with an encapsulated tablet versus the newly developed combination product.
The purpose of this study is not to determine bioequivalence, but to explore

the pharmacokinetic profiles of both administration methods. Additionally, this study explores the speed in which the testosterone dissolves in the mouth by measuring the time the mint flavor is gone.

Study objective

Primary objective:

To compare the pharmacokinetics of testosterone and sildenafil citrate following administration of a sublingual solution of testosterone with an encapsulated tablet versus a combination product.

Secondary objective:

To investigate the time frame in which the mint flavored testosterone coating is dissolved.

Study design

This is a single-center, randomized, cross-over controlled study with two pharmaceutical formulations containing testosterone and sildenafil citrate.
A total of 12 subjects receive each investigational drug product once in random order, so that 6 subjects will start with the first formulation and 6 subjects with the second formulation.
Wash-out between treatments will be at least 7 days. Baseline pharmacokinetic assessments will be performed each experimental visit before each dosing. Pharmacokinetic assessments will be performed at pre-determined time points. Subjects visit the site a total of 4 times: 1 day screening (V0), 2 admission period and 1 follow up visit. During all visits the subjects* health will be monitored.

Intervention

Two interventions will be performed on all participants:
- Administration of sublingual testosterone (0.5 mg) and an oral tablet containing sildenafil (50 mg).
- Administration of a single fixed-combination oral tablet containing 0.5 mg testosterone and 50 mg sildenafil

Following drug administration, blood samles will be taken at several times (29 in total) during the day in order to determine the pharmacokinetic profiles of the two formulations.

Study burden and risks

General

The subjects will receive reimbursement of expenses for participation. A standard reimbursement of 828 Euros is given for study completion. Travel expenses are also reimbursed (fixed fee, 38 Euros).

Blood sampling
A total amount of 453.2 ml will be drawn in each included subject during the course of the experiment.

Medication
The main adverse reactions to exogenous androgens given chronically in physiological to slightly supraphysiological concentrations are androgenic side effects, primarily hirsutism and acne. We consider it to be highly unlikely that testosterone administration in the doses and frequency to be used in this study will give rise to any serious health risks. In our previous studies, no serious health risks/adverse reactions were observed. Within 15 minutes of testosterone (0.5 mg, sublingually) intake plasma testosterone concentration increased 10-fold, and returned to baseline levels within 150 minutes.(Tuiten et al., 2000, van Rooij et al., in preparation). Testosterone is administered over two experimental visits with a 7 day wash-out between the experimental visits. The dosing regime regarding testosterone is therefore considered to be safe.
The most commonly reported adverse reactions in sildenafil treated patients (based on almost 9000 patients) were headache, flushing, dyspepsia, visual disorders, nasal congestion, dizziness and visual colour distortion (website medicines.org). Sildenafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The total body clearance of sildenafil is 41 l/h with a resultant terminal phase half life of 3-5 h.
There are no reports of serious health risks of studies which investigated the combination of testosterone (dosed as gels or via patches) and sildenafil. Furthermore, in our previous studies no serious adverse events were attributed to the use of the combination of testosterone and sildenafil. Most common adverse events were minor headaches and flushing.
Data on the effect of sildenafil and testosterone on oral contraceptives is lacking. For this reason, participants on oral contraceptives will be instructed to use a second anti-conception method (double barrier). All participants will be instructed not to become pregnant during the study.

Clinically relevant abnormalities in ECG and chemistry may be noticed, in which case a medical specialist may be asked for advice, upon decision of the research team. If the specialist confirms that medical treatment is necessary, the participant*s GP physician will be informed. This procedure is mandatory

and explained to the subject in the Informed Consent form.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Provision of written informed consent
2. Female 18-35 years of age
3. Healthy based on medical history, physical examination, laboratory values and vital signs
4. Body mass index (BMI) >= 18 kg/m2 and <= 30 kg/m2
5. Venous access sufficient to allow blood sampling as per protocol

Exclusion criteria

Cardiovascular conditions
1. Any underlying cardiovascular condition, including unstable angina pectoris
2. History of myocardial infarction, stroke, or life-threatening arrhythmia within the prior 6 months
3. Uncontrolled atrial fibrillation/flutter at screening, or other significant abnormality observed on electrocardiogram (ECG)
4. Systolic blood pressure >= 140 mmHg and/or diastolic blood pressure > 90 mmHg.
5. Systolic blood pressure < 90 mmHg and/or diastolic blood pressure <50 mmHg;Gynecological and obstetric conditions
6. Use of oral contraceptive containing anti-androgens
7. Use of oral contraceptive containing estrogen or more
8. Pregnancy or intention to become pregnant during this study (Note: An urine pregnancy test will be performed in all women prior to the administration of study medications.)
9. Lactating or delivery in the previous 6 months
10. Unexplained gynecological complaints, such as clinically relevant abnormal uterine bleeding patterns
11. Subjects with a perimenopausal hormonal status (follicle-stimulating hormone>30);Other medical conditions
12. Liver- and/or renal insufficiency
13. Current clinically relevant endocrine disease
14. Current clinically relevant neurological disease which, in the opinion of investigator, would compromise the validity of study results, or which could form a contraindication for sildenafil and/or testosterone use
15. (A history of) hormone-dependant malignancy;Psychological/psychiatric factors
16. A substance abuse disorder that, in the opinion of the investigator, is likely to affect the subject's ability to complete the study or precludes the subject*s participation in the study; mild or moderate alcohol consumption is allowed but must be stopped 24 hours before the experimental visit. Recreational drug use is not allowed beginning 3 weeks before the start of the experimental visit until follow up. Smoking is not allowed. ;Concomitant medication
17. Subjects who are taking CYP3A4-inhibitors (eg, ritonavir, ketoconazol, itraconazol claritromycine, erytromycine and saquinavir)
18. Subjects who are taking CYP3A4-inducers (eg, carbamazepine, fenytoïne, fenobarbital, st Johns Wort, rifampicine)
19. Use of nitrates or nitric oxide donor compounds
20. Use of any other medication that interferes with study medication (eg, monoamine oxidase (MAO) inhibitors (includes classic MAO inhibitors and linezolid), calcium channel blockers (eg, diltiazem and verapamil), use of corticosteroids)
21. Use of testosterone therapy within 6 months before study entry;Drug/food interaction
22. Consumption of grapefruit or grapefruit-containing foods throughout the duration of the study;General
23. Illiteracy, unwillingness, or inability to follow study procedures
24. Any other clinically significant abnormality or condition which, in the opinion of investigator, might interfere with the participant*s ability to provide informed consent or comply with study instructions, compromise the validity of study results, or be a

contraindication for sildenafil and/or testosterone use.
25. Participation in any other clinical drug study in the previous 3 months.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-05-2011
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lybrido fixed-combination tablet
Generic name:	Lybrido fixed-combination tablet
Product type:	Medicine
Brand name:	testosterone
Generic name:	testosterone
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Viagra
Generic name:	sildenafil
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-02-2011
Application type:	First submission
Review commission:	METC Twente (Enschede)
Approved WMO Date:	20-05-2011
Application type:	First submission
Review commission:	METC Twente (Enschede)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-000457-23-NL
CCMO	NL35616.044.11