A randomized, open label balanced two period, two-treatment, two-sequence crossover study to evaluate the effect of food on the pharmacokinetics of sildenafil after a single oral administration of Lybrido in healthy female subjects

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Primary objective1. To determine the effect of food on the pharmacokinetics of sildenafil administered as the Lybrido formulation2. To determine whether >90% of the testosterone content is released after maximally 90 seconds after sublingual...

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

Summary

ID

NL-OMON41076

Source
ToetsingOnline

Brief title
Lybrido Food Effect

Condition

- Sexual dysfunctions, disturbances and gender identity disorders

Synonym
problems with sexual functioning, Sexual dysfunction

Research involving
Human

Sponsors and support

Primary sponsor: EB FlevoResearch BV
Source(s) of monetary or material Support: EB FSD BV

Intervention

Keyword: Female Sexual Dysfunction, Lybrido, Randomized, Sildenafil

Outcome measures

Primary outcome

Pharmacokinetic

90% CI ratio for both AUCinf and Cmax

Secondary outcome

Pharmacokinetic

Difference in Tmax and tlag

and

- Area under the concentration time curve (AUC)

- Peak exposure (Cmax)

- Time to peak exposure (Tmax)

- Lag time (tlag)

- Terminal elimination half-life (t*)

Residual testosterone per tablet and rupture test analysis after:

A. 30 sec sublingual administration

B. 60 sec sublingual administration

C. 90 sec sublingual administration

D. 120 sec sublingual administration

Safety

E. Nature, frequency and severity of adverse events

F. Vital signs and 12-lead ECG

G. Safety laboratory tests (urinalysis, hematology, biochemistry)

Study description

Background summary

Background
Sexual dysfunction
In many mammalian species, female sex steroids are necessary for the expression of female sexual behavior. In most animals, copulation is limited to the period of ovulation. Humans (as well as higher primates), however, show sexual intercourse also outside the periovulatory period. Testosterone is clearly involved in female sexual behavior. A complete loss, decreased libido, or absence of desire for sexual activity is common after bilateral oophorectomy, adrenalectomy, and after natural menopause, while substitution with testosterone has been shown to improve sexual motivation and performance.

The 3 (transitional and overlapping) phases of the human sexual response can each be disrupted, leading to low sexual desire, sexual arousal problems, and hampered orgasm. The phases are regulated by relatively independent neurotransmitter functions, and dysfunctions may be amenable to psychopharmacological treatment. Traditionally, motivated behaviors have been divided into appetitive and consummatory components. Activities aimed at obtaining reward and satisfactions belong to the appetitive component. The fundamental appetitive motivational process is an intrinsic brain function and is especially related to the predictive value of stimuli for reward.
Processing of motivationally relevant information (i.e., stimuli predicting reward) causes an increase in activity of the meso-accumbens dopaminergic system (i.e., dopamine neurons of the ventral tegmental area [VTA] innervating the nucleus accumbens). The activity of this system is increased during flexible approach behavior when anticipating reward related to copulation. Increasing activity in these dopaminergic pathways facilitates sexual motivation, in particular anticipatory sexual behavior.

Anticipating sexual reward will produce arousal of the genitals, in which at least 2 key neurotransmitters are involved: acetylcholine and nitric oxide (NO). Acetylcholine and NO both promote erections in men and lubrication and swelling in women. Orgasm, the consummatory phase of human sexual response, is facilitated by descending spinal noradrenergic fibers and innervation of the genitals, and inhibited by descending spinal serotonergic fibers.

Study objective

Primary objective
1. To determine the effect of food on the pharmacokinetics of sildenafil administered as the Lybrido formulation
2. To determine whether >90% of the testosterone content is released after maximally 90 seconds after sublingual dosing

Secondary objective
1. To evaluate the safety and tolerability of a single dose of Lybrido under fasted and fed conditions

Study design

This will be a randomized, open-label balanced two-period, two-treatment, two-sequence crossover study in healthy female subjects to evaluate the effect of food on the pharmacokinetics (PK) of sildenafil after a single dose of Lybrido. In addition, safety and tolerability of Lybrido administered after fed and fasted conditions will be evaluated. Furthermore, in vivo confirmation of testosterone release and dissolution time of will be assessed.

All subjects will complete a screening visit. Prior to the day of dosing, eligible subjects will stay overnight (O/N) (at least 10 hours) in an environment controlled for fasting conditions.
The subjects will be randomized to one of the following treatments:
H. Lybrido under fed conditions
I. Lybrido under fasted conditions

On the day of dosing, subjects in treatment A will take a high fat, high calorie meal (50% of the caloric intake of 800-1000 kcal) on site. The drug is administered 30 minutes after the start of the food intake and the meal should be completed within this 30 minutes time frame. No intake of water is allowed the hour prior to and 1 hour post administration of the drug. Drug will be taken with 240 mL water and subject will abstain from food intake the following 4 hours. The food intake will be standardized for all patients during 12 hours post dose.

For subjects in treatment B, administration of the drug is taken with 240 mL water. No intake of water is allowed the hour prior to and 1 hour post

administration of the drug. Next 4 hours, the subject will abstain from food intake. The food intake will be standardized for all patients during 12 hours post dose.

Both periods will be separated by a washout period of at least 1 week between the dosing of the 1st period and dosing of the 2nd period.

After the last blood sample on day 2, the subjects will hold another Lybrido tablet sublingually for a defined time (30, 60, 90 or 120 seconds) after which the tablet is not swallowed but accurately collected in a tube for further analysis of testosterone content.

Intervention

NA

Study burden and risks

NA

Contacts

Public
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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. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study;
2. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures;
3. Females between 18 and 55 years of age (both inclusive);
4. Healthy based on medical history, physical examination, electrocardiogram, laboratory values and vital signs;
5. Body mass index (BMI) >=18 kg/m2 and <= 30 kg/m2;
6. Venous access sufficient to allow blood sampling as per protocol;

Exclusion criteria

Cardiovascular conditions;
1. History of myocardial infarction, stroke, transient ischemic attack, or life-threatening arrhythmia within the prior 6 months;
2. Uncontrolled atrial fibrillation/flutter at screening or other significant abnormality as observed on electrocardiogram (ECG);
3. Systolic blood pressure >= 140 mmHg and/or diastolic blood pressure >= 90 mmHg;
4. Systolic blood pressure < 90 mmHg and/or diastolic blood pressure< 50 mmHg;
5. Use of oral contraceptives containing anti-androgens (e.g. crypteron acetate) or anti (androgenic) progestogens (drosperidone, dienogest, chlormadinone acetate and norgestrel);6. Use of any hormone replacement therapy (HRT) containing more than 50 µg/day of estrogen;
7. Pregnancy (note: an urine pregnancy test will be performed in all women prior to the administration of study medication);
8. Lactating or delivery in the previous 6 months;
9. Perimenopausal status (cycle shortening/irregular menstrual bleeding in the last 12 consecutive months and/or occurrence of vasomotor symptoms (e.g. hot flashes, night contraceptive sweating) in combination with elevated FSH levels (>40 IU/L) for women age 40 onwards; in women with a history of hysterectomy, perimenopausality can be assessed by FSH levels (>40 IU/L) and/or vasomotor symptoms);
10. Liver and/or renal insufficiency;
11. Current clinically relevant endocrine disease;
12. Positive serology for HIV, Hepatitis B (surface antigen), and/or Hepatitis C;
13. Substance abuse disorder;

14. Use of nitrates or nitric oxide donor compounds;
15. Subjects who are taking potent CYP3A4 inhibitors or inducers;
16. Use of serotonergic drugs (e.g. Trazodon, fluvoxamide);17. Use of testosterone therapy within 6 months before study entry;
18. Use of any medication that interferes with study medication (e.g. monoamine oxidase (MAO) inhibitors, calcium channel blockers);
19. Illiteracy, unwillingness or inability to follow study procedures;
20. Participation in any other clinical drug study in the previous 3 months;

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-06-2014
Enrollment:	18
Type:	Actual

Medical products/devices used

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:	17-06-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-06-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 25592
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2014-001944-38-NL
CCMO	NL49313.056.14
OMON	NL-OMON25592