Two-Center, In-Patient, Randomized, Placebo and Active Comparator Evaluation of the Pharmacokinetics (PK) and Safety, Along with Initial Pharmacodynamic (PD) Efficacy of Three Dose Levels of TBS-2 Intranasal Gel Applied Twice-Daily (BID) for up to Three Days in Female Patients with Hypoactive Sexual Desire Disorder (HSDD) or Anorgasmia (ANOR).

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This clinical trial is being performed to evaluate the PK profile of TBS-2 administered as single and multiple (BID) doses in patients with HSDD or ANOR. In addition, the study will evaluate the initial PD efficacy and safety of intranasal TBS-2 BID...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Endocrine disorders of gonadal function
Study type	Interventional

Summary

ID

NL-OMON34282

Source
ToetsingOnline

Brief title
Eval. PK /Safety of TBS-2 Intranasal in Fem. Pat. with HSDD/ANOR

Condition

- Endocrine disorders of gonadal function
- Sexual dysfunctions, disturbances and gender identity disorders
- Sexual function and fertility disorders

Synonym
Hypoactive Sexual Desire Disorder and Anorgasmia

Research involving
Human

Sponsors and support

Primary sponsor: Trimel Biopharma SRL
Source(s) of monetary or material Support: Trimel Biopharma SRL

Intervention

Keyword: Evaluation, Female Patients, PK and Safety, TBS-2 Intranasal Gel

Outcome measures

Primary outcome

Primary end-point:

a) To evaluate the PK profile of TBS-2 administered BID in patients with HSDD

or ANOR.

The serum concentrations of total testosterone and dihydrotestosterone will be

measured using validated LC/MS/MS. The following pharmacokinetic parameters

will be determined for all subjects:

- Cmin, Cmax, tmax, PTF and PTS will be determined, for each dosing interval

- AUC0-*, and Cavg, will be calculated for each dosing interval.

- The percentage of time within, below, and above the physiological reference range for serum testosterone and dihydrotestosterone.

Secondary outcome

Secondary end-points:

a) To evaluate the initial PD efficacy of TBS-2 administered BID in patients with HSDD or ANOR.

- Efficacy will be determined by a battery of computer and psychophysiological tests.

b) To evaluate the safety of intranasal TBS-2 BID versus Intrinsa ® patch in patients with HSDD or placebo in patients with ANOR.

- Erythrocytosis, anemia, and infections will be monitored by measuring complete blood counts at Baseline and the Close-Out Visit.
- Clinical chemistry and urinalysis testing at Baseline and Close-Out will assess selected endocrine parameters, renal function, liver function (hepato-cellular or obstructive liver disease), skeletal/heart muscle damage, lipid abnormalities, and changes in calcium homeostasis.
- Measurement of serum testosterone, dihydrotestosterone and various hormones at Baseline, study days and Close-Out will allow for determinations of treatment-associated laboratory shifts, if present.
- Adverse Events.

Study description

Background summary

In contrast to the role in men, the function of testosterone in women has not been investigated as thoroughly as that of estrogen and progesterone. Studies that have investigated the conversion of testosterone to dihydrotestosterone (DHT) in women in comparison to men (Mahoudeau, Bardin, Lipsett. 1971) or the daily testosterone synthesis in women and men, indicate that the synthesis in women is approximately one tenth that observed in men (Korenman, Wilson, Lipsett. 1963).

The concentrations of testosterone, its precursors, and metabolites decrease significantly in women aged 30-40 years (Labrie, Luu-The, Labrie et al. 2003). In contrast to the abrupt decline in estrogens and progesterone after the menopause, the decline of testosterone is more gradual over a longer period in the pre-menopause (Padero, Bhasin, & Friedman. 2002), indicating that the decline in testosterone production is a phenomenon of an overall aging process, and not primarily a result of a menopausal decline in ovarian testosterone production. In addition, the data show that free testosterone is the more suitable measure of androgen homeostasis in women. In the postmenopausal woman, testosterone levels are approximately one half of that observed in young women, primarily due to a decrease in the production of adrenal androgen precursors. The interpretation of the androgen status in postmenopausal women is further complicated by the fact that the majority of biologically active androgen in these women is synthesized from inactive precursors such as DHEA and DHEA-S in the peripheral tissues and may act in those tissues in a paracrine or intracrine fashion with only the testosterone metabolites appearing in the serum (Labrie, Luu-The, Labrie et al. 2003).

More recent studies indicate that testosterone plays an important physiological role in women regarding their mood, body composition, bone health, physical and mental strength and sexual function (Davis 1999). A consensus conference held in Princeton in 2001 defined the clinical construct of an androgen insufficiency syndrome and recommended a trial of testosterone therapy for women fulfilling the criteria (Bachmann, Bancroft, Braunstein, et al. 2002). A position paper from the North American Menopause Society has made a similar recommendation (Menopause 2005), although a position paper from the Endocrine Society recommended that more research be performed before testosterone is used as part of the hormone treatment of postmenopausal women (Wierman, Basson, Davis, et al. 2006).

At present the only registered indication of testosterone administration in women is the treatment of FSD after surgical menopause. Studies carried out on women with surgical or natural menopause who fulfil the definition of

hypoactive sexual desire disorder (HSDD) have shown that the administration of exogenous testosterone through the oral, transdermal or parental route with or without concomitant estrogen therapy results in an increase in desire, arousal, frequency of satisfactory sexual activity, pleasure, and responsiveness (Braunstein, 2006; Alexande, Dennerstein, Burger, et al. 2006; Somboonporn, 2006).

Study objective

This clinical trial is being performed to evaluate the PK profile of TBS-2 administered as single and multiple (BID) doses in patients with HSDD or ANOR. In addition, the study will evaluate the initial PD efficacy and safety of intranasal TBS-2 BID and compare the safety to Intrinsa in the HSDD population and to placebo in the ANOR population. PD efficacy will be determined using implicit as well as psychophysiological tests. These tests have shown to discriminate between women with acquired HSDD and controls. Recently, automatic affective associations with sexual stimuli were assessed in premenopausal US and Dutch women with acquired HSDD (n = 42) and a control group of sexually functional women (n = 42) using two implicit tasks (single target Implicit Association Task and the Picture Association Task). Results of both tasks showed that women with acquired HSDD displayed less positive automatic associations with sexual stimuli than sexually functional women (Brauer, van Leeuwen, Janssen, et al. submitted). A dot-probe task assessing attentional preference for sexual and neutral visual stimuli did not discriminate between groups, but was found to be sensitive to testosterone in earlier studies, and will therefore be used as well (van der Made, Bloemers, Yassem, et al. 2009; van der Made, Bloemers, van Ham, et al. 2009).

In the same sample of premenopausal US and Dutch women, HSDD-women*s genital (VPA- vaginal pulse amplitude) response and reports of subjective sexual arousal to low, medium and high-intensity erotic film stimuli were significantly lower than those of sexually functional women (Laan, Brauer, Janssen, et al in preparation). Psychophysiological testing in the present study will therefore involve assessment of vaginal pulse amplitude (VPA) and subjective sexual arousal during sexual to self-induced erotic fantasy, a low-intensity erotic film clip, and a high-intensity erotic film clip. Psychophysiological testing will take place 0.5 hours and 4.5 hours after dosing. The rationale for this repeated testing is based on a 4-hour delay effect of testosterone on VPA (Tuiten, Van Honk, Koppeschaar, et al. 2000; Tuiten, Van Honk, Verbaten, et al. 2002). This finding was replicated in another laboratory (Heard-Davison, Heiman, Kuffel. 2007).

Study design

This is a Phase I, two-center, randomized, placebo-controlled and double-blind (ANOR arms), parallel-groups, 4-arm (equal balance), active-controlled (HSDD

arms) study in female patients. Both pre- and post- menopausal women will be enrolled in the ANOR cohort for the TBS-2 treatment arms (with a majority of the patients pre-menopausal). Only post-menopausal women will be randomized into the HSDD cohort.

Intervention

TBS-2 intranasal gel or Intrinsa transdermal patch

Study burden and risks

Please refer to the relevant pages of the study protocol.

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

Females up to 65 years
HSDD with personal distress
BMI equal to or less than 35
Women must have a score of >11 on the FSDS-R

Exclusion criteria

History of any clinically relevant other psychiatric disorders that could impact sexual function
History of Major Depressive Disorder within 6 months prior to study
Patients who meet DSM-IV criteria for Sexual Aversion Disorder, Substance-Induced Sexual Dysfunction, Dyspareunia (not caused by inadequate foreplay stimulation or alleviated by lubricants), Vaginismus, Gender Identity Disorder, Paraphilia, or for Sexual Dysfunction Due to a General Medical Condition.
Patients with pelvic inflammatory disease, urinary tract or vaginal infection

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-09-2010
Enrollment:	48
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Intranasal Testosterone Gel
Generic name:	Intranasal Testosterone Gel
Product type:	Medicine
Brand name:	Intrinsa 300 micrograms/24 hours transdermal patch
Generic name:	Testosterone transdermal patch
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-06-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-08-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2010-020396-22-NL

Register	ID
CCMO	NL32667.058.10