CLINICAL TRIAL REPORT

A double-blind, placebo controlled single centre trial to evaluate the dose-relationship of the effects of vaginally administered oxytocin on the vaginal mucosal membrane in postmenopausal women with vaginal atrophy

Protocol number:	OXYPEP002
EudraCT number:	2011-005465-20
Trial development phase:	II
Tested drug substance:	Vagitocin (oxytocin gel)
Proposed indication:	Vaginal atrophy
Date of report:	2013-02-08
Sponsor:	PeP-Tonic Medical AB
First patient enrolled (date):	2012-02-15
Last patient completed (date):	2012-07-27
Principal investigator:	Aino Fianu Jonasson, Karolinska University Hospital, Huddinge
Sponsor's CEO:	Dan Markusson, PeP-Tonic Medical AB
CRO contact person:	Johannes Molin, Pharma Consulting Group in Uppsala AB

1. SIGNATURES

Trial title: A double-blind, placebo controlled single centre trial to evaluate the dose-relationship of the effects of vaginally administered oxytocin on the vaginal mucosal membrane in postmenopausal women with vaginal atrophy

Report No.: OXYPEP002

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the trial.

Principal Investigator:

Aino Fianu Jonasson, Associate professor, MD, PhD — Date
Karolinska University Hospital, Huddinge

Sponsor's Representative:

Dan Markusson, CEO — 2013-02-12
PeP-Tonic Medical AB — Date

Biostatistician:

Kerstin Wiklund, VP Biometrics — Date
Pharma Consulting Group AB

Medical Writer:

Rose-Marie Lindgren, Senior Clinical Research Associate — Date
Pharma Consulting Group AB

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Principal Investigator:

Aino Fianu Jonasson, Associate professor, MD, PhD — Date: 13 feb. 2013
Karolinska University Hospital, Huddinge

Sponsor's Representative:

Dan Markusson, CEO — Date
PeP-Tonic Medical AB

Biostatistician:

Kerstin Wiklund, VP Biometrics — Date: 2013-02-18
Pharma Consulting Group AB

Medical Writer:

Rose-Marie Lindgren, Senior Clinical Research Associate — Date: 15 Feb 2013
Pharma Consulting Group AB

2. SYNOPSIS

Name of Sponsor/Company:
PeP-Tonic Medical AB, Växjö, Sweden

Name of Finished Product:
Vagitocin

Name of Active Ingredient:
Oxytocin

Title of Study:
A double-blind, placebo controlled single centre trial to evaluate the dose-relationship of the effects of vaginally administered oxytocin on the vaginal mucosal membrane in postmenopausal women with vaginal atrophy

Investigator:
Aino Fianu Jonasson, Karolinska University Hospital, Huddinge, Stockholm, Sweden

Study Centre:
Kvinnokliniken, Karolinska University Hospital, Huddinge, Stockholm, Sweden

Publication (reference):
Not applicable.

Studied period:	**Phase of development:**
2012-02-15 (date of first enrolment) 2012-07-27 (date of last completed)	II

Objectives:
Primary objective:
To investigate the dose-relationship of topical Vagitocin on the vaginal mucosal membrane.
Safety objectives:
To investigate the safety and tolerability of topical Vagitocin treatment.

Methodology:
Double-blind, randomised placebo controlled trial, with a parallel design.

Number of patients (planned and analysed):

	Vagitocin, 100 IU	Vagitocin, 400 IU	Placebo	Total
Planned:	24 (100%)	24 (100%)	16 (100%)	64 (100%)
Randomised and treated:	24 (100%)	24 (100%)	16 (100%)	64 (100%)
Completed:	18 (75.0%)	23 (95.8%)	14 (87.5%)	55 (85.9%)
Analysed for efficacy:				
Full analysis set	24 (100%)	24 (100%)	16 (100%)	64 (100%)
Per protocol analysis set	17 (70.8%)	23 (95.8%)	14 (87.5%)	54 (84.4%)
Analysed for safety:	24 (100%)	24 (100%)	16 (100%)	64 (100%)
Baseline values:				
Females	24	24	16	64
Mean age (range)	62.0 (52, 75)	61.1 (52, 73)	63.2 (55, 75)	62.0 (52, 75)

Diagnosis and main criteria for inclusion:
Diagnosis: Vaginal atrophy

Inclusion criteria:

1. Naturally postmenopausal or ooforectomized women, completely without menstrual bleedings for at least four years prior to baseline.
2. > 40 years of age.
3. Moderate to severe symptoms of at least one of the following criteria of vulvar and vaginal atrophy associated with the menopause, according to the patient's self-assessment: vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, vaginal pain associated with sexual activity, or presence of vaginal bleeding associated with sexual activity.
4. Atrophic mucosa according to the investigator's assessment.
5. Signed Informed Consent.

Exclusion criteria:

1. Usage of any sex steroids including phytoestrogens, hormonal intra-uterine device or herbal medicinal products with known estrogenic effects within 3 months prior to baseline.
2. Usage of any lubricant for intra-vaginal administration at baseline.
3. Vaginal bleeding of unknown origin.
4. Vaginal pH ≤ 5.0.[1]
5. Any ongoing uro-genital infection within 7 days prior to baseline.
6. Body Mass Index (BMI) >30 kg/m2.
7. Systolic Blood Pressure > 150 mmHg and Diastolic Blood Pressure > 90 mmHg at baseline.
8. Any concurrent malignant disease as judged by the investigator.
9. Clinically significant medical history (excluding medically well-controlled hypertension and hypercholesterolemia), abnormal findings from physical examinations, vital signs, cytology, histology, US examination of uterus and ovaries or laboratory analyses that may interfere with the trial objectives or compromise the safety of the patient as judged by the investigator.
10. Concurrent and diagnosed nephrological or hepatic disorder
11. Diagnosed with HIV, Hepatitis B or C
12. Known or suspected drug or alcohol abuse, within 12 months prior to baseline.
13. Known or suspected allergy to any ingredient of the trial product.
14. Incapacity to perform trial procedures, as judged by the investigator.
15. Participation in any other interventional clinical trial within 3 months prior to baseline

There were also specific reasons for discontinuing a patient from further assessments based on results from the baseline visit as follows:

- Cervical cytology assessed during the baseline visit ≥ CIN1
- FSH plasma levels <40 IU/L and 17β-estradiol levels ≥70pmol/L at the baseline visit
- ≥5% superficial cells at the baseline visit

[1] Exclusion criterion no. 4 removed, Amendment 2, 2012-02-28

Test product, dose and mode of administration, batch number:
Vagitocin (oxytocin gel) in two different strengths (100 IU and 400 IU), topically administered once daily during 7 weeks. Batch numbers: XB1201, XB1102

Duration of treatment:
Topically administered once daily during 7 weeks.

Reference therapy, dose and mode of administration, batch number:
Placebo, gel with the same composition, appearance as the test product, topically administered once daily during 7 weeks. Batch numbers: XB1201, XB1102

Criteria for evaluation:

Primary efficacy endpoint:

- Change in percentage points of superficial cells from Baseline visit (visit 1) to 7 weeks of treatment (Visit 3).

Secondary efficacy endpoints:

- Change in percentage points of superficial cells from Baseline visit to 2 (Visit 2) weeks of treatment.
- Change in maturation value from Baseline visit to 2 (Visit 2) and 7 (Visit 3) weeks of treatment.
- Change in vaginal pH from Baseline visit to 2 (Visit 2) and 7 (Visit 3) weeks of treatment.
- Visual appearance of the vaginal mucosa after 2 (Visit 2) and 7 (Visit 3) weeks of treatment
- Patients´ self-assessment of the most bothersome symptom after 2 (Visit 2), 7 (Visit 3), weeks of treatment and at the telephone follow-up after 9 weeks.
- Histological assessment after 2 (Visit 2) and 7 weeks (Visit 3) of treatment.
- Change in score in selected items of WHQ/SSP from Baseline visit to 7 (Visit 3) weeks of treatment and at the telephone follow-up after 9 weeks.

Safety

Safety endpoints:

- Incident and severity of reported adverse events (AEs) and endometrial biopsy and ultrasound evaluation of endometrial thickness in order to exclude any potential endometria malignancies or hyperplasia.

Statistical methods:
Efficacy endpoints: The primary efficacy variable was analysed with analysis of covariance (ANCOVA) in a pre-specified hierarchical structure.
The secondary endpoints, change in percentage points of superficial cells (from baseline to Visit 2), change in maturation value, change in vaginal pH and QoL score in selected items of WHQ/SSP were analysed as the primary efficacy variable. Visual appearance of the vaginal mucosa, patients´ self-assessment of the most bothersome symptom and histological assessment were tested with a logistic regression model of polytomous response. If the proportional odds assumption could not be satisfied, treatment comparisons were done using a Cochran-Mantel-Haenszel (CMH) nonzero correlation test. All models included treatment group and baseline value.

Safety endpoints:
Incidence of AEs and SAEs in each MedDRA SOC and PT was presented by treatment group and in total. Incidence of AEs was also summarised at SOC and PT level in terms of intensity and relationship to IMP by treatment group.
Vital signs, laboratory tests, cervical cytology and oxytocin plasma concentration were summarised by treatment group for each visit.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

The primary objective with this dose-finding study was to investigate the dose-relationship of two oxytocin concentrations applied in an intravaginal gel (Vagitocin) for treatment of vaginal atrophy.

No statistically significant differences between the active treatment and placebo groups were achieved for cytological and histological parameters. As this may be due to the small number of patients participating in the study complementary statistical analyses were performed. When the effect of Vagitocin was tested within groups significant effects were observed on all cytological, histological and clinical parameters, whereas no such effects were found in the placebo group.

Vagitocin (400 IU) displayed a statistically significant effect (p= 0.009) on the most bothersome symptom after 7 weeks of treatment. Thus, more than half of the patients reported a considerable reduction in the perception of the most bothersome symptom, while rather few did so in the placebo group.

In order to demonstrate the effectiveness of Vagitocin versus placebo, the effect size of active treatment and placebo was compared for 15 different variables. The effect of Vagitocin (400 IU) was larger in 14 out of 15 of these variables, which corresponds to a significant difference at the level of p of 0.001.

Based on the results obtained in the WHQ and SSP questionnaires it could be stated that women treated with Vagitocin experienced themselves as more self secure, as having access to more energy, as being more relaxed, less stressed and more socially interactive than those receiving placebo. In addition they experienced more wellbeing when compared to those women being treated with placebo. These differences were highly significant and always in favour of oxytocin treatment in spite of the fact that a relatively small group of women participated in the study.

Taken together these results indicate that Vagitocin induces at least 3 important clinical effects in the context of menopausal disorders. Vagitocin stimulates the growth of the cells in the vaginal epithelium thereby restoring the atrophic vaginal mucosa by an effect exerted locally in the vagina. Vagitocin profoundly decreases menopausal symptoms in particular the experience of the most bothersome symptom. Vagitocin induces an increased sense of wellbeing, gives more psychic energy, improves social performance and reduces anxiety.

SAFETY RESULTS:

- In total, there were 41 reported AEs for 27 patients (42.2%). Of the 41 AEs, 17 AEs were reported by 12 patients (50%) treated with Vagitocin 100 IU, 16 AEs were reported in 10 patients (41.7%) treated with Vagitocin 400 IU and 8 AEs reported in 5 (31.3%) of the placebo patients. Thirty-seven (37) patients (57.8%) did not report any AEs.
- High mean oxytocin plasma concentrations were observed after dosing (highest at 30 min post-dose) for both the Vagitocin treatment groups. The indicated absorption through the vaginal mucosa was not expected, since the Vagitocin formulation had been changed since previous trial.
- There were no deaths, other SAEs or other AEs judged as significant reported in the trial. Two patients withdrew from the trial due to AEs; palpitation (judged as moderate intensity, possible relationship to trial treatment) was the reported AEs. Both were recovered after four and six days duration, respectively.
- The most common SOC for AEs reported was Infections and infestations where 12 patients (18.8 %) reported 15 AEs. The most common PT reported, for this SOC, was Urinary tract infection with six reported AEs in five patients (7.8%), all in the active treatment groups, followed by Influenza with four reported AEs in four patients (6.3%) and Nasopharyngitis with three reported AEs in three patients (4.7%).
- There were two AEs, judged to be of severe intensity, Gastroenteritis and Headache, reported in one patient. The relationship was unrelated for 15 patients (24 AEs) and possible for 12 patients (17 AEs). No AEs with probable relationship to the trial treatment were reported.