ABBREVIATED CLINICAL STUDY REPORT

A Phase 2b, Double-blind, Randomised, Parallel, Placebo-Controlled Study to Evaluate the 12-week Efficacy of Vagitocin in Postmenopausal Women with Symptoms of Vulvovaginal Atrophy

Sponsor Code:	OXYPEP202
EudraCT Number:	2016-000158-36
Report Version and Date:	Final version 1.0, 2017-08-18
Phase:	Phase IIb
Test Product/Device:	Vagitocin (Oxytocin gel)
Proposed Indication:	Vulvovaginal Atrophy
Coordinating Principal Investigator:	Aino Fianu Jonasson, Karolinska Universitetssjukhuset, Huddinge, Sweden
Sponsor:	PEPTONIC medical AB
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Contract Research Organisation:	PCG Clinical Services AB Kungsängsvägen 19 753 23 Uppsala, Sweden Phone: +46 18 430 3100
Main Part of the Study	
First Subject Screened:	2016-04-19
Last Subject Last Visit:	2017-02-15
Exploratory Part of the Study	
First Subject Screened:	2016-10-26
Last Subject Last Visit:	2017-04-19

1 SIGNATURES

Study Title: A Phase 2b, Double-blind, Randomised, Parallel, Placebo-Controlled Study to Evaluate the 12-week Efficacy of Vagitocin in Postmenopausal Women with Symptoms of Vulvovaginal Atrophy

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

Coordinating Principal Investigator:

Aino Fianu Jonasson, MD, PhD,
Karolinska Universitetssjukhuset, Huddinge

2017-08-28
Date

Sponsor's Representative:

Dan Markusson, COO
PEPTONIC medical AB

2017-08-23
Date

Biostatistician(s):

Johanna Tilly, MSc, Senior Biostatistician,
PCG Clinical Services AB

2017-08-29
Date

2 SYNOPSIS

Name of sponsor/company:

PEPTONIC medical AB

Name of finished product:

Vagitocin

Name of active ingredient:

Oxytocin

Study title:

A Phase 2b, Double-blind, Randomised, Parallel, Placebo-Controlled Study to Evaluate the 12-week Efficacy of Vagitocin in Postmenopausal Women with Symptoms of Vulvovaginal Atrophy

Coordinating principal investigator:

Aino Fianu Jonasson,
Karolinska Universitetssjukhuset, Huddinge, Sweden

Study centres:

- Karolinska Universitetssjukhuset, Huddinge, Sweden
- Akademiska Sjukhuset, Uppsala, Sweden
- Norrlands Universitetssjukhus, Umeå, Sweden

Publication(s) based on the study (reference):

Not applicable

Studied period:	**Phase of development:**
Main part: • First subject screened: 2016-04-19 • Last subject last visit: 2017-02-15 Exploratory part: • First subject screened: 2016-10-26 • Last subject last visit: 2017-04-19	Phase IIb

Objectives:

Primary objective
To evaluate the efficacy of Vagitocin in reducing the severity of the most bothersome symptom (MBS) of vulvovaginal atrophy (VVA) associated with menopause after 12 weeks of treatment.

Secondary objective
To evaluate safety and tolerability of 400 IU of Vagitocin.

Exploratory objectives:
To evaluate the efficacy, safety and tolerability of Vagitocin administered by 2 different applicators.
To evaluate plasma levels of oxytocin after administration of 400 IU of Vagitocin by 2 different applicators.

Study design:

This was a 12 week, multi-centre, randomised, parallel group, double-blind, placebo controlled Phase 2b study divided in 2 parts: the main part and the exploratory part.

Examination of the results from the primary and some secondary efficacy endpoints of the main part of the study (vaginal pH, % superficial cells and VVA symptoms [including the MBS]) showed that treatment with Vagitocin had no significant effect compared to placebo (i.e. no clinical endpoints were met). For this reason, it was decided by the Sponsor to create an abbreviated clinical study report (CSR).

Name of sponsor/company: PEPTONIC medical AB
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All the safety endpoints, for both the main and exploratory parts of the study, are reported in this abbreviated CSR. The following were removed from the planned analysis and are not reported in this CSR: remaining efficacy secondary endpoints for the main part of the study, all efficacy endpoints of the exploratory part of the study and oxytocin plasma concentration levels for either the main or exploratory parts of the study. The main part of the study investigated the efficacy and safety of oxytocin gel (Vagitocin) intravaginally administered in glass syringes on postmenopausal women with VVA symptoms (vulvar/vaginal irritation and itching, vaginal dryness, dysuria, dyspareunia or presence of vaginal bleeding associated with vaginal sexual activity [yes/no]). One hundred and sixty subjects were planned to be enrolled (actual: 161 subjects) and randomised to 2 treatment groups: Vagitocin (planned: 80 subjects, actual: 81 subjects) and placebo (planned: 80 subjects, actual: 80 subjects). The exploratory part of the study was to investigate the efficacy and safety of Vagitocin intravaginally administered in a laminate tube on postmenopausal women. However, the exploratory efficacy endpoints were removed from the planned analysis and are not reported in this CSR. Forty subjects were planned to be enrolled in the exploratory part (actual: 41 subjects) and randomised to 2 treatment groups: Vagitocin (planned: 30 subjects, actual: 31 subjects) and placebo (planned: 10 subjects, actual: 10 subjects). In addition, a comparison of the plasma levels of oxytocin when Vagitocin was administered by 2 different applicators (glass syringes and laminate tubes) was to be investigated in a sub-group of all subjects. However, this was removed from the planned analysis and is not reported in this CSR. The study was conducted in 3 sites in Sweden and comprised of 5 visits: Screening visit/Week -3 to Week 0 (Visit 0), Randomisation visit/Week 0 (Visit 1), Treatment follow-up visit/Week 4 (Visit 2), End-of-treatment Visit/Week 12 (Visit 3) and a Telephone follow-up visit/Week 14 (Visit 4). All subjects were to self-administer an intravaginal gel (1 × 1 mL active or placebo) once daily for 12 weeks. The first dose of study medication was self-administered at the site under the supervision of the study personnel. Subjects were provided with enough study medication until the next scheduled visit and were instructed by the staff at the clinical site on how to administer the study treatment once a day at bedtime at approximately the same time for 12 weeks.

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Number of female subjects (planned and analysed):

Main part of the study

	Total	Vagitocin	Placebo
Number of subjects planned:	160	80	80
Number of subjects randomised:	161	81	80
Mean age (range) years:	58.3 (49 -65)	58.0 (49 - 65)	58.7 (53 - 65)
Number of subjects analysed for efficacy:			
Modified intention-to-treat (mITT):	157	79	78
Per protocol (PP):	153	76	77
Number of subjects. analysed for safety:	161	81	80
Number of subjects completed the study as per protocol:	157	78	79

Exploratory part of the study

	Total	Vagitocin	Placebo
Number of subjects planned:	40	30	10
Number of subjects randomised and treated:	41	31	10
Mean age (range) years:	57.1 (52 - 65)	57.1 (53 - 64)	57.2 (52 - 65)
Number of subjects. analysed for safety:	41	31	10
Number of subjects completed the study as per protocol:	39	30	9

Diagnosis and main criteria for inclusion:

Diagnosis: Vulvovaginal atrophy.

Females aged 40-65 years who were either postmenopausal or had undergone surgical bilateral oophorectomy, with ≤5% superficial cells in vaginal smear cytology, a vaginal pH >5.0, a body mass index (BMI) ≤32 kg/m^2, an endometrial thickness of <4 mm and one moderate to severe VVA symptom but who were otherwise in good health and had provided signed informed consent were considered eligible to participate in the study.

Test product, dose and mode of administration, batch number:

Vagitocin vaginal gel (1 x 1 mL/400 IU) daily for 12 weeks administered intravaginally. Batch numbers (finished product): 3046999, 3047171 and 3047616 (main part) and 3049358 (exploratory part)

Reference product, dose and mode of administration, batch number:

Placebo vaginal gel (1 x 1 mL), with the same composition, appearance and route of administration as the test product, daily for 12 weeks administered intravaginally. Batch numbers (finished product): 3046877, 3047170 and 3047652 (main part) and 3049357 (exploratory part).

Duration of treatment:

Product was administered once daily for 12 weeks.

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Efficacy assessments:
Efficacy measurements, reported in this CSR, include: evaluation of VVA symptoms (including the MBS), assessments of vaginal pH and vaginal cytology (% superficial cells).

Primary efficacy endpoint

- Change from baseline to Week 12 in severity of the VVA symptom that has been self-identified by the subject as being the MBS to her at baseline.

Secondary efficacy endpoints (reported in this CSR)

- Change from baseline to Week 4 and Week 12 in vaginal pH.
- Change from baseline to Week 4 and Week 12 in % superficial cells.
- Change from baseline to Week 4 in severity of the VVA symptom that has been self-identified by the subject as being the MBS to her at baseline.
- Change from baseline to Week 4 and Week 12 in severity of individual VVA symptoms.

Note that change from baseline to Week 12 in vaginal pH and in % superficial cells are considered main secondary endpoints.

Secondary efficacy endpoints (not reported in this CSR)

- Change from baseline to Week 4 and Week 12 in % parabasal cells.
- Change from baseline to Week 4 and Week 12 in maturation value.
- Change from baseline to Week 4 and Week 12 in summary score 1 for the VVA symptoms vulvar/vaginal irritation and itching, dyspareunia, vaginal dryness and dysuria.
- Change from baseline to Week 4 and Week 12 in summary score 2 for the VVA symptoms vulvar/vaginal irritation and itching, dyspareunia, vaginal dryness and dysuria.
- Change from baseline to Week 12 in quality of life (QoL) evaluation parameters.
- Change from baseline to Week 12 in body weight.

Exploratory efficacy endpoints (not reported in this CSR)

- Plasma concentrations of oxytocin administered by 2 different applicators.
- Efficacy of oxytocin administered via the laminate tube (the same efficacy endpoints as for the main part of the study).

Safety assessments:
The safety measurements included: adverse events (AEs), vital signs, physical examinations, gynaecological examinations, breast examinations, laboratory tests, transvaginal ultrasound (including endometrial thickness) and Pap smear.

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Safety endpoints Change from baseline over time of clinical safety data: AEs, vital signs, physical examination findings, gynaecological examination findings, breast examination findings, laboratory tests, transvaginal ultrasound and Pap smear.
Statistical methods: Continuous data are summarised using descriptive statistics and categorical data are presented using frequency (n) and percentage (%). Nominal (i.e. unadjusted for multiplicity) two-sided p-values at the 5% significance level are presented. Efficacy analyses were performed using both the modified intent-to-treat (mITT) and the per-protocol (PP) populations. The mITT population is the main efficacy population. The PP population was used for sensitivity analyses of the efficacy endpoints. Safety analyses were performed using the safety population. There is 1 set of populations for each part of the study (main part and exploratory part). Primary endpoint: A Cochran-Mantel-Haenszel test using modified ridit scores (Wilcoxon rank sum test) adjusted for the baseline value was performed. Secondary endpoints (reported in this CSR): Change from baseline in vaginal pH was analysed with an analysis of covariance (ANCOVA) model where the model included treatment group and baseline value. Change from baseline in % superficial cells was analysed using a logistic regression model where treatment group and baseline value are included, together with descriptive summaries of when % superficial cells are not equal to zero. Change from baseline to Week 4 in severity of the VVA symptoms that has been self-identified by the subject as being the MBS to her at baseline, and change from baseline to Week 4 and Week 12 in severity of individual VVA symptoms were analysed using the same method as used for the primary endpoint. Summaries are presented to describe the characteristics of reported AEs and include: the number and percentage of subjects who reported at least 1 AE and the number of events reported by severity, seriousness, and relationship to study medication. A summary of AE system organ class (SOC) and preferred terms (PTs) are presented. Laboratory test results and vital signs descriptive summaries are included for each evaluation, as well as change from baseline. Physical examination, gynaecological, breast examinations, transvaginal ultrasound and Pap smear are summarised by visit and as shift tables by treatment group. Endometrial thickness is summarised as result and as change from baseline for each visit by treatment group. The study was to be considered successful if the two-sided p-value in the statistical analysis of the primary endpoint for the main study was less than 0.0500 and in favour of the active treatment. However, the main secondary endpoints for the main study were also of importance.

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Summary of results

Efficacy results:

- There was no statistically significant difference between the Vagitocin and placebo groups in change from baseline to Week 12/Visit 3 in severity of the most bothersome VVA symptom for either of the mITT or PP population. Descriptive data showed a decrease in the severity of the MBS in both treatment groups at Week 12/Visit 3 (Vagitocin: 72.2% of subjects, placebo: 76.9% of subjects), indicating a positive effect of both treatments.
- There was no statistically significant difference between the 2 treatment groups in change from baseline to either Week 4/Visit 2 or Week 12/Visit 3 in vaginal pH. Descriptive data showed a decrease from baseline in mean (standard deviation [SD]) values in both treatment groups at Week 4/Visit 2 (Vagitocin: 0.38 [0.95], placebo: -0.53 [1.02]) and Week 12/Visit 3 (Vagitocin: -0.46 [1.00], placebo: 0.73 [1.08]), indicating a positive effect of both treatments.
- There was no statistically significant difference between the 2 treatment groups in change from baseline to either Week 4/Visit 2 or Week 12/Visit 3 in % superficial cells. Descriptive data showed an increase from baseline in mean (SD) values in both treatment groups at Week 4/Visit 2 (Vagitocin: 2.90 [8.88], placebo: 2.39 [8.27]) and Week 12/Visit 3 (Vagitocin: 3.77 [9.49], placebo: 1.94 [5.12]), indicating a positive effect of both treatments.
- There was no statistically significant difference between the 2 treatment groups in change from baseline to Week 4/Visit 2 in severity of the most bothersome VVA symptom. Descriptive data showed a decrease in the severity of the MBS in both treatment groups at Week 4/Visit 2 (Vagitocin: 59.5% of subjects, placebo: 62.8% of subjects), indicating a positive effect of both treatments.
- There was no statistically significant difference between the 2 treatment groups in change from baseline to Week 4/Visit 2 or Week 12/Visit 3 in severity of any individual VVA symptom (vaginal dryness, vulvar/vaginal irritation and itching, dysuria, dyspareunia or absence or presence of vaginal bleeding associated with vaginal sexual activity).

Safety results:
Main part of the study

- The mean (SD) number of days subjects were exposed to investigational medicinal product (IMP) treatment was comparable in the 2 treatment groups: 82.8 (7.2) days for the Vagitocin group and 84.0 (7.2) days for the placebo group.
- Fifty-nine subjects (36.6%) reported a total of 88 AEs. Thirty-two subjects (39.5%) in the Vagitocin group reported 49 AEs and 27 subjects (33.8%) in the placebo group reported 39 AEs. There were no AEs that lead to death.
- A total of 3 serious AEs (SAEs) (2 subjects) were reported: 1 SAE in the Vagitocin group (breast cancer, assessed as unlikely related to the IMP) and 2 associated SAEs in the placebo group (fall and rib fracture, both assessed as not related to the IMP).
- Three AEs lead to withdrawal of 3 subjects from the Vagitocin group: vulvovaginal burning sensation (assessed unlikely related to the IMP), atrial fibrillation (assessed as not related to the IMP), vulvovaginal candidiasis (assessed as possibly related to the IMP). These AEs but 1 (atrial fibrillation) were deemed as resolved by the time of study end.

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- Most AEs (86 out of 88 AEs) were assessed as mild to moderate and were distributed evenly in the 2 treatment groups.
- Approximately one third of AEs (32 out of 88 AEs) were assessed as possibly or probably related to the IMP. The most commonly reported being vaginal discharge and vaginal odour.
- The most frequently reported AEs were: vaginal discharge (reported by 7.5% of subjects), urinary tract infection (reported by 4.3% of subjects) and vaginal odour (reported by 4.3% of subjects). About twice as many subjects reported these AEs in the Vagitocin group as compared to the placebo group.
- There were no safety and tolerability concerns based on vital signs, physical examinations and clinical laboratory evaluations. Occasional abnormal, clinically significant (CS) findings were noted.
- There were no safety and tolerability concerns based on gynaecological examinations, breast examinations, transvaginal ultrasound (including endometrial thickness) and Pap smear evaluations. Occasional abnormal, CS findings were noted.

Exploratory part of the study

- The mean (SD) number of days subjects were exposed to IMP treatment was comparable in the 2 treatment groups: 81.8 (14.3) days for the Vagitocin group and 81.6 (7.4) days for the placebo group.
- Nineteen subjects (46.3%) reported a total of 32 AEs. Thirteen subjects (41.9%) in the Vagitocin group reported 20 AEs and 6 subjects (60.0%) in the placebo group reported 12 AEs.
- There were no AEs that lead to death and no SAEs were reported.
- Two AEs lead to withdrawal of 2 subjects: influenza (placebo) assessed as not related to the IMP and vulvovaginal burning sensation (Vagitocin) assessed as possibly related to the IMP. These AEs were deemed as resolved by time of study end.
- Most AEs (31 out of 32 AEs) were assessed as mild to moderate.
- Approximately half of AEs (14 out of 32 AEs) were assessed as possibly or probably related to the IMP. The most commonly reported being vaginal odour.
- The most frequently reported AEs were: vaginal odour (reported by 9.8% of subjects), vaginal discharge (reported by 7.3% of subjects), influenza (reported by 7.3% of subjects), nasopharyngitis (reported by 7.3% of subjects) and urinary tract infection (reported by 4.9% of subjects).
- There were no safety and tolerability concerns based on vital signs, physical examinations and clinical laboratory evaluations. Occasional abnormal, CS findings were noted.
- There were no safety and tolerability concerns based on gynaecological examinations, breast examinations, transvaginal ultrasound (including endometrial thickness) and Pap smear evaluations. Occasional abnormal, CS findings were noted.

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Overall Conclusions: • There were no significant differences between Vagitocin and placebo regarding the effect of reducing the severity of the most bothersome VVA symptom after 12 weeks of treatment. There was also no statistically significant difference between Vagitocin and placebo on the effect on vaginal pH or % superficial cells. • Both Vagitocin and placebo treatments improved the severity of the most bothersome VVA symptom, vaginal pH and % superficial cells compared with baseline levels. • There were no safety or tolerability concerns in this study when subjects were treated with either Vagitocin or placebo gels intravaginally administered in glass syringes. • There were no safety or tolerability concerns in this study when subjects were treated with either Vagitocin or placebo gels intravaginally administered in laminate tubes.