2 SYNOPSIS

Name of Sponsor / Company: Bionorica SE	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: na		
Name of Active Ingredient: VAC BNO 1095 10 mg FCT		

Title of clinical trial:

Prospective, double-blind, placebo-controlled, parallel-group, multi-centre, randomized clinical trial to proof efficacy and safety of 20 mg (2 tablets of 10 mg) VAC BNO 1095 FCT in patients suffering from cyclic mastodynia and PMS

Investigators:

[redacted]

Clinical Trial Centres:

25 investigational sites were approved by the EC (7 sites in DE & 18 sites in PL).
22 investigational sites were initiated (5 sites in DE & 17 sites in PL).
17 investigational sites were actively recruiting patients (3 sites in DE & 14 sites in PL).
For details please see below:

[redacted]

Publication (Reference):

None

Studied Period (months): Date of First Enrolment: Date of Last Completed:	5 complete menstrual cycles for each patient 6 JUN 2013 20 OCT 2014	Phase of Development: III

Objectives:

To prove the efficacy and safety of 20 mg (2 tablets of 10 mg) VAC BNO 1095 FCT in the treatment of cyclic mastodynia

Methodology:

The trial was designed as a Phase III, randomised, placebo-controlled, double blind, multi-centre, parallel-group trial investigating the efficacy and safety of VAC BNO 1095 FCT.
The clinical part of the trial duration was maximum 143 days with 3 visits in Run-In phase (visit S-2, S-1, V0) and 3 visits in treatment phase (visits V1, V2, V3).
The screening visit (S-2) was performed 2 complete cycles plus an undefined number of days prior to the onset of the first menstruation before patient's randomisation to the treatment on baseline V0.
To evaluate the **cyclic mastodynia**, the breast pain severity was self-assessed daily by the patient by means of a VAS (Visual Analogue Scale). Breast pain intensity had to reach ≥ 50 (of a maximum of 100 which had to response to 100 mm on a hard-copy VAS) on the VAS on at least one of the 5 days of the late luteal phase *[changed by the Amended Clinical Trial Protocol 4.0 to 7 days]* of both Run-In-cycles, corresponding to moderate to severe cyclic mastodynia. In addition, in order to prove the cyclic course of mastodynia, the VAS in the mid follicular phase (maximum value of 5 daily recordings *[changed by the Amended Clinical Trial Protocol 4.0 to 7 days]*) had to be less than 75 % of the VAS in the late luteal phase (maximum value of 5 daily recordings *[changed by the Amended Clinical Trial Protocol 4.0 to 7 days]*) in both Run-In cycles.
To evaluate **PMS (Premenstrual Syndrome)**, eligible patients had to report at screening PMS lead symptoms of severity moderate or severe, and had to prove in both run-in cycles a cyclic course according to ACOG criteria and a minimum symptom severity defined by a sum score of 20 in COPE *[changed by the Amended Clinical Trial Protocol 4.0 to (…) eligible patients had to report at screening PMS lead symptoms. For both run-in cycles, patients had to fulfil the PMS criteria according to ACOG criteria: PMS sum score resulting from COPE in the mid follicular phase (sum score of all PMS sum scores across the seven-day phase) had to be less than 75 % of the PMS sum score resulting from COPE in the late luteal phase (sum score of all PMS sum scores across the seven-day phase)]*.
Patients who meet criteria for diagnosis of PMDD were excluded. Additionally a clinical breast and physical examination were performed and patients signed in and started a PMS symptom / VAS.
At baseline visit V0, patients who did not meet specific chosen exclusion criteria were enrolled in the trial and randomised to either placebo or verum group.
The severity of **cyclic mastodynia** was recorded daily throughout the 3-cycle treatment period. At the end of the treatment cycle (cycles 1 and 2 for the secondary endpoints; cycle 3 for the primary endpoint) the maximum and the average cyclic mastodynia value of the late luteal phase were used as efficacy endpoints and the maximum and the average cyclic mastodynia value, respectively, of the late luteal phase of the 2nd Run-In cycles were used as baseline covariate during evaluation.
PMS symptoms were recorded daily throughout the Run-In and treatment phase by means of the COPE in the e-diary. Scores obtained during the late luteal phases of treatment cycles were evaluated, the scores obtained during the late luteal phases of the 2nd Run-In cycle were used as baseline covariate.

Number of Patients:

Planned: 280 patients were required to be screened to achieve 220 patients eligible for randomisation (110 to each treatment group), of which 160 (80 per group) were expected to be available for data evaluation
Randomized and analysed (per treatment group):

Randomized	VAC BNO 1095		Placebo		Screening failure		Total	
	N	%	N	%	N	%	N	%
No	.	0.0	.	0.0	85	100.0	85	88.5
Yes	4	100.0	7	100.0	.	0.0	11	11.5

Randomized	4	7	11
SEP	4	7	11
FAS	4	6	10
PP	n.a.	n.a.	n.a.

SEP = safety evaluable population; FAS = full analysis set; PP = per protocol population; n.a. = not applicable

Diagnosis:

Female patients suffering from cyclic mastodynia and PMS excluding PMDD

Main Criteria for inclusion:

1. Females aged 18 to 45 who have signed an ICF at screening V S-2 at the latest
2. Patient had a history of cyclic mastodynia and PMS at V S-2
3. Stable cycle duration of 25 to 35 days during the past 6 months before screening V S-2 and during Run-In phase
4. At screening V S 2 patient was reporting at least one physical PMS symptom rated moderate or severe (lead symptom requiring treatment) and one psychic symptom for the late luteal phase of the preceding cycle, using the COPE symptom list
5. At screening V S-2 patient reported symptoms of a total score of at least 15 in the late luteal phase of the preceding cycle, using the COPE symptom list

6. In both run-in cycles:
   A. VAS ≥ 50 at least on one of the days of the late luteal phase
   B. Cyclic course of the mastodynia, i.e. VAS in the mid follicular phase (maximum value of 5 daily recordings) is less than 75 % of the VAS in the late luteal phase (maximum value of 5 daily recordings [*changed by the Amended Clinical Trial Protocol 4.0 to: 7 daily recordings*])
   C. PMS sum score resulting from COPE had to be 20.0 or more in the late luteal phase (average of daily recordings documented on days 5 to 1) *[This inclusion criterion was deleted by the Amended Clinical Trial Protocol 4.0]*
   D. At least one physical PMS symptom had to be rated moderate or severe on at least one day of the late luteal phase, and one psychic symptom was present *[changed by the Amended Clinical Trial Protocol 4.0 to: At least one physical PMS symptom and one psychic symptom was present on at least one day of the late luteal phase]*
   E. PMS sum score resulting from COPE must not exceed 10 at day 4 of the menstruation *[This inclusion criterion was deleted by the Amended Clinical Trial Protocol 4.0]*
   F. PMS sum score resulting from COPE must not exceed 8.0 in the mid follicular phase (average of daily recordings documented on days 6 to 10) [*changed by the Amended Clinical Trial Protocol 4.0 to: PMS sum score resulting from COPE in the mid follicular phase (sum score of all PMS sum scores across the seven-day phase) is less than 75 % of the PMS sum score resulting from COPE in the late luteal phase (sum score of all PMS sum scores across the seven-day phase)]*

   Note: "Late luteal phase" was defined as days -5 to -1 (5 days prior to the onset of menses) while "mid follicular phase" is defined as days 6 to 10 after the onset of menses [*changed by the Amended Clinical Trial Protocol 4.0 to: "Late luteal phase" was defined as days -7 to -1 (7 days prior to the onset of menses) while "mid follicular phase" was defined as days 3 to 9 after the onset of menses].*
7. Compliance for keeping detailed symptom records was expected
8. Patient provided a negative pregnancy test at study start (V S 2, V0 and V3 if of childbearing potential) and was willing to use one of the following hormone-free medically acknowledged contraception methods with a PEARL-index < 1 % from enrolment till onset of next menses after study termination:
   - Double-barrier method, e.g. condom* and occlusive cap (diaphragm or Portio cap or Lea Contraceptivum) with spermicidal foam/gel/film/cream/suppository (* A female condom and a male condom had not be used together as friction between the two could result in product failing), or
   - hormone-free intra uterine device (IUD) and condom, or
   - hormone-free IUD and sponge, or
   - hormone-free IUD and spermicidal foam/gel/film/cream/suppository or
   - vasectomized partner or
   - sexual abstinence

   Non childbearing potential group was defined for the intended patient as surgical sterilisation at least three months before the start of the study
9. An unsuspicious breast USG/mammogram not older than 12 months ruling out signs of malignancy was available (otherwise arrangement of a breast USG prior to V S 1, exceptionally prior to V0)

Test Product:	VAC BNO 1095 10 mg FCT
Mode of Administration:	oral
Dose:	2 tablets in the morning for 3 menstrual cycles (i.e. for 84 days in case of 28 days of cycle duration)
Batch Number (blinded):	0000069703

Reference Product:	Placebo
Mode of Administration:	oral
Dose:	2 tablets in the morning for 3 menstrual cycles (i.e. for 84 days in case of 28 days of cycle duration)
Batch Number (blinded):	0000069703

Dose Regime:

Patients were randomly assigned to one of the blinded treatment groups:
Group 1: VAC BNO 1095 2x10 mg FCT: 2 tablets in the morning
Group 2: Placebo: 2 tablets in the morning

Duration of Treatment:

The duration of both, trial drug and placebo treatment periods, was 3 menstrual cycles (i.e. 84 days in case of 28 days of cycle duration) in both treatment groups.

Criteria for Evaluation:

Efficacy

PRIMARY EFFICACY ENDPOINT

Maximum severity of cyclic breast pain (cyclic mastodynia) during the late luteal phase of the 3rd treatment cycle under Investigational Medicinal Product (IMP). The severity of cyclic breast pain was self-assessed by the patient on a Visual Analogue Scale (VAS).

SECONDARY EFFICACY ENDPOINTS

1. Maximum severity of cyclic breast pain (cyclic mastodynia) during the late luteal phases of treatment cycles 1 and 2. The severity of cyclic breast pain was self-assessed by the patient on a Visual Analogue Scale (VAS).
2. Average severity of cyclic mastodynia, determined in the late luteal phase of each of the treatment cycles.
3. Intensity of premenstrual syndrome (PMS) assessed by means of a premenstrual symptom diary (COPE = calendar of premenstrual experiences) during each of the treatment cycles.
4. Overall assessments of efficacy on cyclic mastodynia and PMS by patient and investigator at study end (visit V3) by a score ranging from 1 to 5.
5. Subgroup analysis:
   A. Patients with the waist circumference ≤ 90 cm
   B. Patients with the waist circumference > 90 cm
   For both subgroups A. and B.: Maximum severity of cyclic breast pain (cyclic mastodynia) during the late luteal phase of the 3rd treatment cycle under Investigational Medicinal Product (IMP). The severity of cyclic breast pain was self-assessed by the patient on a VAS.

Safety

Incidence and intensity of adverse events were assessed during the study from spontaneous reporting of the patient as well as from changes in health status, concomitant diseases and therapies observed / diagnosed by the investigator as well as clinically relevant changes in laboratory parameters.
Changes in laboratory parameters between (V S-1) and (V3), i.e. prior and after the treatment period, were evaluated, independently of their potential classification as adverse event.
Vital signs - blood pressure (mmHg), heart rate (bpm) were assessed at V S-2 and V3.
Overall tolerability was assessed by patient and investigator at study end by a score ranging from 1 to 5.

Statistical Methods:

The safety population (SEP) included all randomised patients with at least one documented application of the investigational drug and post-baseline safety data.
The Full Analysis Set (FAS) for the efficacy analyses included all randomised patients with at least one documented application of the investigational drug and post-baseline efficacy data.
The Per-Protocol (PP) population for the efficacy analyses would have included all FAS patients who did not show protocol deviations which could have had a relevant influence on the assessment of the primary efficacy endpoint.
Because of the premature stop of the trial due to the low number of randomized patients no PP evaluation was performed and only basic tables and listings were evaluated using the Safety Evaluable Population (SEP) and Full Analysis Set" (FAS). Therefore all Protocol Deviations (PD) are identified but not assessed for allocation of patient to Per Protocol Set (PP) before breaking the blind of the treatment code.

Summary – Conclusions:

In general the conclusion of the efficacy/safety results is very limited due to the very low number of randomized patients (4 patients in the verum group VAC BNO 1095 vs. 6 patients in the placebo group).

EFFICACY RESULTS:

Primary efficacy endpoint

The mean maximum severity of cyclic breast pain was lower under placebo treatment compared to VAC BNO 1095 (43.0 vs. 52.0, respectively).

Secondary efficacy endpoints

In VAC BNO 1095 group mean severity of breast pain only slightly lowered in cycle C3 and C4 (47.8 and 47.5, respectively) as well as in placebo group (50.8 and 50.3, respectively).
The decrease in average severity in time period C3 to C5 was higher in the placebo group than in the verum group (-6.9 vs. -1.4).
Comparing the intensity of PMS on C3 and C5 the mean COPE symptom score was -4.7 during treatment with placebo and +1.9 during treatment with VAC BNO 1095.
Patient and investigator assessed the efficacy on cyclic mastodynia and PMS equally as "very good", "good" and "moderate" for VAC BNO 1095 treatment and "very good", "good" and "poor" for placebo treatment.
The treatment with VAC BNO 1095 was not superior over placebo at the primary endpoint and all secondary endpoints. The standard deviation (SD) was high in all results.

SAFETY RESULTS:

Adverse events

Overall, the number of patients reporting at least one AE was higher in placebo group than in VAC BNO 1095 group (3 patients vs. 1 patient, respectively). During the trial 10 AEs occurred, 80% in placebo group. Due to the low number of patients no most commonly reported AE occurred. One patient of the placebo group had increased liver enzymes (4 out of 10 AEs) but had a medical history of increased liver enzymes 3.5 years prior inclusion into the trial. In placebo group, resolution of 2 AEs was unknown at study end and both AEs were still ongoing. The outcome was unknown in 3 AEs (1 AE in verum group, 2 ongoing AEs in placebo group). The intensity of AEs was judged as mild or moderate (6 vs. 4 AEs, respectively). No severe AE was reported. In total, 4 AEs (Abdominal pain upper, Acne, Gamma-glutamyltransferase increased, Blood triglycerides increased) were judged by the investigators as related to study medication; all 4 ARs occurred in the placebo group. Both AEs occurring under treatment with VAC BNO 1095 (Ovarian cyst, Anaemia) were judged as not related to study medication by the investigators. No AE required a change of trial medication.
In total, one serious AE (SAE) "ovarian cyst" leading to hospitalization was reported under treatment with VAC BNO 1095. The SAE resolved and did not result in a temporary or permanent discontinuation of trial medication. The investigator considered the SAE as "not related" to investigational treatment.

Safety laboratory

In one patient of the placebo group clinically relevant abnormalities were evaluated wherefore corresponding AEs were documented. All other mean values of the evaluated laboratory parameters showed no medically relevant changes.

Tolerability of treatment assessed by investigator and patient

The tolerability of the treatment with VAC BNO 1095 did not differ as it was assessed as "very good' by both investigator and patient (100.0%). Both the investigators and patients assessed the tolerability of placebo as "good" (40.0%) or "very good" (60.0%).

Pregnancy

One patient became pregnant during intake of placebo and prematurely terminated the trial for that reason. She delivered twins without complications or malformations even though preterm.

CONCLUSION:

The clinical trial seemed to fail to show superiority over placebo at the primary endpoint as the mean maximum severity of cyclic breast pain was lower under placebo treatment compared to VAC BNO 1095 (43.0 vs. 52.0, respectively). **However, one needs to consider the very low number of the FAS (4 patients in the VAC BNO 1095 vs. 6 patients in the placebo group).**
And also the secondary endpoints, mean and average severity of cyclic breast pain and intensity of PMS assessed by COPE, did not meet the objective of the trial.
The investigational treatments were safe and well tolerated. VAC BNO 1095 and placebo had a comparable safety profile, the judgements by investigators and patients were slightly better for VAC BNO 1095 treatment.
Overall, due to the high screening failure rate and the low number of randomized and treated patients leading to the premature discontinuation of the clinical trial, no conclusion can be made about the evaluated efficacy and safety results.

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