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: VAC BNO 1095 FCT 10 mg		
Name of Active Ingredient: Chaste tree fruit (Vitex agnus castus, fructus)		

Title of Study:

Double-blind comparison of VAC BNO 1095 FCT with placebo to identify dose dependent effects in patients suffering from cyclic mastodynia and PMS

Design of Study:

Randomised, prospective, double-blind, placebo-controlled, multicentre, parallel group phase III study

Investigators:

[redacted]

Study Centre(s):

The 11 initiated centres in Czech Republic were active.

Publication (reference):

None

Studied Period (years): Date of First Enrolment: Date of Last Completed:	approx. 10 months 08 MAR 2011 10 JAN 2012	Phase of Development: III

Objectives:

Identification of the optimal dosage of VAC BNO 1095 FCT for treatment of cyclic mastodynia and PMS.
To prove the efficacy and safety of VAC BNO 1095 FCT in the treatment of cyclic mastodynia.

Methodology:

The trial was designed as a randomised, prospective, double-blind, placebo-controlled, multi-centre, parallel groups phase-III study to identify the optimal dosage of VAC BNO 1095 FCT for treatment of cyclic mastodynia and PMS, and to prove the efficacy of VAC BNO 1095 FCT (1x10 mg and 2x10 mg per day respectively) in the treatment of cyclic mastodynia compared to placebo.

The scheduled study duration for each patient was approximately 140 days (5 cycles of 28 days each), depending on individual cycle duration.

The study consist of a run-in phase with 2 screening visits (covering 2 menstrual cycles in order to prove cyclic mastodynia and PMS) and 1 Baseline visit, and a treatment phase with 3 follow-up visits under treatment (covering 3 cycles). After first screening visit S-2 further visits were scheduled after the end of each of the 2 run-in cycles (visit S-1 [Day -28 of study] and Baseline visit V0 [Day 0 of study]), and after the first (visit V1 [Day 28 of study]), second (visit V2 [Day 56 of study]) and third treatment cycle (visit V3 [Day 84]), respectively. Visits were performed during the menses, at Day 3 of each mensis, i.e. 2 days after Day 1 of the respective menstruation, with exception of the

screening visit which could be performed at any time prior to the first run-in cycle. A tolerance limit of -1 to +3 days was given for all visits.

At V0, female patients who meet all inclusion and none of the exclusion criteria were randomly (ratio 1:1:1) assigned to one of the three double-blinded treatment groups (Group 1: 1x10 mg VAC BNO 1095, Group 2: 2x10 mg VAC BNO 1095, Group 3: Placebo). Drug supply for the treatment period of one cycle was handed over to the patients at V0, V1 and V2, respectively. The patients were advised to take the study medication in the morning and in the evening. Treatment started on the day of V0 at home. The treatment duration was three cycles of approximately 28 days, each (i.e. about 84 days in total), depending on the individual cycle duration. Drug compliance was checked by the investigator at visits V1, V2 and V3. At V3, investigator and patient assessed the overall efficacy and tolerability of the investigational drug treatment by using a 5-point rating scale (1="very good", 2="good", 3="moderate", 4="poor", 5="very poor").

In a diary, the patient recorded the intensity of their mastodynia by means of a Visual Analogue Scale (VAS), a non-calibrated vertical line in a length of 100 mm (100 mm="unbearable pain", 0 mm ="no pain"), and of their PMS symptoms by means of the COPE (calendar of premenstrual experiences) using a 4-point rating scale (0="not present", 1="mild", 2="moderate", 3="severe"). The assessment was done daily in the evening of each day throughout the run-in and treatment phase (5 cycles). The patient filled in for each of the 5 cycles a separate dairy starting at the 1st day of menstruation. The self-assessment of breast pain severity and PMS symptoms during the 2-cycle run-in period was used to check for patients' enrolment qualification (inclusion/exclusion criteria). Additionally, the efficacy evaluation were planned to be done by comparing the assessments in the COPE and VAS diary of the run-in phase with assessments of the treatment phase.

Blood and urine samples were taken for safety laboratory (biochemistry including prolactin serum level, haematology, and urinalysis) at visits S-2 and V3. Additionally, systolic and diastolic blood pressure [mmHg] and pulse rate [bpm] were measured at S-2 and V3.

S-2 Day -56 (-T*)	*S-1* Day -28 (-1+3 d)	*V0* Day 0 (-1+3 d)	*V1* Day 28 (-1+3 d)	*V2* Day 56 (-1+3 d)	*V3* Day 84 (-1+3 d)	*Assessments and examinations*
x						Demographic data; relevant medical history and current diseases/ conditions; prior and concomitant medication and therapies
x	x	x				Inclusion/exclusion criteria
x	x	x				Criteria for cyclic mastodynia/PMS
x					x	Clinical breast examination
(x[1])						Breast ultrasound
x[2]					x	Physical examination (including blood pressure, pulse rate)
x					x	Sampling for safety laboratory (haematology, biochemistry, urinalysis)
			x	x	x	Adverse events
x	x	x	x	x	x	Concomitant medication and diseases
			x	x	x	Drug compliance
					x	Investigator's and patient's overall assessment on efficacy and tolerability

* T = any period before start of the first menstruation.
[1] In case breast ultrasonography (USG)/mammogram was older than 12 months.
[2] including measurement of weight and height at visit S-2

Number of Patients

Planned: randomisation of 180 patients (60 per treatment arm)
Screened: 224 patients
Screening failures: 33 patients
Randomised and analysed (per treatment arm):

	VAC BNO 1095 1x10 mg		VAC BNO 1095 2x10 mg		Placebo		Total	
	N	%	N	%	N	%	N	%
Randomised	62	100.0	64	100.0	65	100.0	191	100.0
SEP	62	100.0	64	100.0	65	100.0	191	100.0
FAS	62	100.0	64	100.0	64	98.5	190	99.5
PP	58	93.5	63	98.4	62	95.4	183	95.8

SEP = Safety Evaluable Population; FAS = Full Analysis Set; PP = Per Protocol population

Diagnosis:

Cyclic mastodynia with premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD) excluded

Main Criteria for Inclusion:

1. Females aged 18 to 45 who had signed an informed consent form at screening visit S-2 at the latest.
2. Subject had a history of cyclic mastodynia and PMS.
3. Known stable cycle duration of 25 to 35 days during the past 6 months before screening visit S-2.
4. At screening visit S-2, subject 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 visit S-2, subject was reporting 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 mm for breast pain intensity at least on one of the days of the late luteal phase of cycle 1 and 2, corresponding to moderate to severe mastodynia.
   B. Cyclic course of the mastodynia, i.e. VAS in the mid follicular phase (maximum value of 5 daily recordings) was less than 75% of the VAS in the late luteal phase (maximum value of 5 daily recordings) of cycle 1 and 2, corresponding to an increase of pain severity of at least 33%.
   C. PMS sum score resulting from COPE had to be 20 or more in the late luteal phase (average of daily recordings documented on days -5 to -1).
   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.
   E. PMS sum score resulting from COPE not exceeding 10 at day 4 of the menstruation.
   F. PMS sum score resulting from COPE not exceeding 8 in the mid follicular phase (average of daily recordings documented on days 6 to 10).

   Note: "Late luteal phase" was defined as days –5 to –1 (5 days prior to the onset of menses) while "mid follicular phase" was defined as days 6 to 10 after the onset of menses.
7. Compliance for keeping detailed symptom records could be expected.
8. Subject provided a negative pregnancy test at study start (if of childbearing potential) and used a double-barrier hormone-free medically acknowledged contraception during the whole course of study (condom with spermicidal jelly, foam suppository, or film; diaphragm with spermicide; or condom and diaphragm with spermicide), or a hormone-free intra uterine device.
   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 breast USG had to be arranged prior to visit S-1).

Test Product:	VAC BNO 1095 film-coated tablet 10 mg
Mode of Administration:	Oral
Batch Number (blinded):	0000049960

Placebo for Test Product:	VAC BNO 1095 Placebo film-coated tablet
Mode of Administration:	Oral
Batch Number (blinded):	0000047151

Dose Regimen:

Patients were randomly (1:1:1) assigned to the following blinded treatment groups:

- Group 1 (1x10 mg VAC BNO 1095):
  in the morning: 1x1 tablet 10 mg VAC BNO 1095
  in the evening: 1x1 tablet Placebo
- Group 2 (2x10 mg VAC BNO 1095):
  in the morning: 1x1 tablet 10 mg VAC BNO 1095
  in the evening: 1x1 tablet 10 mg VAC BNO 1095
- Group 3 (Placebo):
  in the morning: 1x1 tablet Placebo
  in the evening: 1x1 tablet Placebo

Duration of Treatment:

Depending on the individual cycle duration, the treatment duration was three cycles of approximately 28 days, each, i.e. about 84 days in total, in all 3 treatment groups.

Criteria for Evaluation:

Efficacy

PRIMARY EFFICACY ENDPOINT

Change in maximum severity of cyclic breast pain (cyclic mastodynia) from Baseline (late luteal phase of 2nd run-in cycle) to V3 (late luteal phase of the 3rd treatment cycle under study medication). The severity of cyclic breast pain

was self-assessed by the patient on a Visual Analogue Scale (VAS).
Note: "Late luteal phase" was defined as days –5 to –1 (5 days prior to the onset of menses) while "mid follicular phase" was defined as days 6 to 10 after the onset of menses.

SECONDARY EFFICACY ENDPOINTS

1. The difference between the lower dosage (1x10 mg) compared to the higher dosage (2x10 mg) of VAC BNO 1095 in the change in maximum severity of breast pain from Baseline (late luteal phase of 2nd run-in cycle) to V3 (late luteal phase after three menstrual cycles under study medication).
2. Changes in maximum severity of cyclic breast pain (cyclic mastodynia) from Baseline (late luteal phase of 2nd run-in cycle) to the late luteal phases of cycles 1 (V1) and 2 (V2). The severity of cyclic breast pain was self-assessed by the patient on a Visual Analogue Scale (VAS).
3. Changes in average severity of cyclic mastodynia, determined in late luteal phase of each of the treatment cycles.
4. Changes in intensity of premenstrual syndrome (PMS) assessed by means of a premenstrual symptom diary (COPE = calendar of premenstrual experiences) from Baseline (2nd run-in cycle) to each of the treatment cycle.
5. Overall assessments of efficacy on cyclic mastodynia and PMS by patient and investigator at study end by a score ranging from 1 to 5.

Safety

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

Statistical Methods:

A blinded interim analysis of the primary endpoint was planned to re-estimate the Mean Square Error (MSE) of the ANOVA - according Kieser and Friede [79] in order to adjust the sample size after about 70% of the planned patient data were available.
Patients with cyclic mastodynia and PMS, at least one documented application of the investigational drug and post-treatment efficacy data (here: with respect to the primary endpoint) were included in the interim analysis.
The difference of the primary efficacy endpoint between each active treatment arm (1x10 mg, 2x10 mg VAC BNO 1095) compared to Placebo was analysed by ANOVA with the factors treatment and centre.
Missing values concerning the primary endpoint were replaced according to the "last observation carried forward (LOCF)" method, where the last available value was used for imputation of a missing value.

For the final analysis, only safety analyses based on the safety evaluable population (SEP) were done. Because of serious doubt in the general validity and credibility of diary data (see Appendix 16.1.14, forensic analysis reports [Sachverständigengutachten] dated on 20 APR 2012 and 22 JUL 2012), the initially planned analyses of primary and secondary efficacy endpoints were not performed.

Continuous variables were described by sample size (N), number of missing values (N_{miss}), mean, standard deviation (SD), minimum, 25%-quantile (Q25%), median, 75%-quantile (Q75%) and maximum separately for treatment groups. Categorical variables were described in contingency tables as absolute numbers and percentages separately for treatment groups.

Tests of safety endpoints were performed either "one-sided" using an α level of 2.5% or "two-sided" using an α level of 5%. The analysis of the safety endpoints was of explorative nature. Therefore, no adjustment of error probability for multiplicity was performed.

AEs were classified according to their start date in "treatment emerged" or "post treatment". Frequency and intensity of (S)AEs in total, and of AEs grouped by MedDRA system organ class were tabulated for each treatment group.

The changes of vital signs (blood pressure, pulse rate) from Baseline to study termination were described and tested for differences between treatment groups by ANOVA with the factors treatment and centre.

Changes in laboratory parameters between visits S-2 and V3, i.e. prior and after the treatment period, were presented by shift-tables.

The presence of a relationship between the dose levels (Placebo, 1x10 mg and 2x10 VAC BNO 1095) and the global tolerability assessed by investigator and patient was tested by Jonckheere-Terpstra Test. Pairwise test was performed by the Wilcoxon Mann Whitney Test accounting for centres (van Elteren's Test).

Summary – Conclusions:

Efficacy Results:

Because of serious doubt in the general validity and credibility of diary data (see Appendix 16.1.14, forensic analysis reports [Sachverständigengutachten] dated on 20 APR 2012 and 22 JUL 2012), the initially planned analyses of primary and secondary efficacy endpoints were not performed.

Safety Results:

The investigational treatments (1x10 mg and 2x10 mg daily dose of VAC BNO 1095 and Placebo) for 3 cycles (about 84 days in total) were shown to be safe and well tolerated.

Adverse events

Overall, the number of patients in the SEP cohort reporting at least 1 AE was 93 out of 191 patients (48.7%) in the treatment phase and 18 out of 191 patients (9.4%) after the treatment phase. No serious AEs were reported during the entire study.

The number of *treatment emerged* AEs was similar during 1x10 mg VAC BNO 1095 and Placebo treatment (50 AEs reported for 28 patients of the 1x10 mg VAC BNO 1095 group and 55 AEs for 31 patients of the Placebo group) but slightly lower compared to 67 AEs reported for 34 patients in the 2x10 mg VAC BNO 1095 group. The frequency of *post treatment* AEs was lower and comparable in the three treatment groups (1x10 mg VAC BNO 1095: 8 AEs reported by 5 patients, 2x10 mg VAC BNO 1095: 15 AEs reported by 7 patients, Placebo: 10 AEs reported by 6 patients).

Treatment emerged AEs affecting 2 or more patients were mainly investigations (162 AEs), followed by skin/subcutaneous tissue disorders and infections/infestations in a clearly lower frequency (each not more than 3 AEs in total). *Post treatment* AEs were investigations (32 AEs) and in a markedly lower frequency blood and lymphatic system disorders (1 AE). Generally, an increase in basophil count and decrease in neutrophil count was observed in all treatment groups at end of treatment phase and during the follow-up.

The intensity of all *post treatment* AEs and the majority of *treatment emerged* AEs was mild. Only, pruritus (Pat./CRF No. 147) and diarrhoea (Pat./CRF No. 279) were of moderate intensity during 1x10 mg VAC BNO 1095 treatment, vaginal infection (Pat./CRF No. 55) during 2x10 mg VAC BNO 1095 treatment as well as cystitis (Pat./CRF No.103) during Placebo treatment. None of the 205 AEs was severe.

All AEs starting during or after 2x10 mg VAC BNO 1095 and Placebo treatment were not related to the study medication. Only during the 1x10 mg VAC BNO 1095, pruritus (Pat./CRF No. 130 and 147) and facial swelling (Pat./CRF No. 147) were classified as related to the study medication. They did not result in a change of study drug regime or any other therapy and were in accordance with the expected safety profile of VAC BNO 1095. At the end of the study, these 3 drug-related AEs were assessed as recovered by the investigator.

None of the reported AEs required a change in the study drug regimen. All *post treatment* AEs and the *majority of AEs* during the treatment phase required no therapy. Only, 5 *treatment emerged* AEs required concomitant medication: headache (Pat./CRF No. 113) and diarrhoea (Pat./CRF No. 279) during 10 mg VAC BNO 1095 treatment, vaginal infection (Pat./CRF No. 55) during 2x10 mg VAC BNO 1095 treatment, cystitis (Pat./CRF No.103) and vaginal infection (Pat./CRF No. 276) during Placebo treatment.

The majority of the *post treatment* AEs and *treatment emerged* AEs were not yet recovered at study end or their outcome was unknown. Only, a low number of the treatment emerged AEs (i.e. all AEs not due to laboratory investigations) but all AEs which were classified as related to the study medication were recovered at the end of the entire study.

Safety laboratory

No clinically relevant abnormalities in urine were determined at Baseline and end of treatment phase.

Mean values of safety parameters from blood analyses (haematology and biochemistry) were within normal range at both time points of measurements before and after treatment phase.

At end of treatment phase, several blood parameters were outside the extended normal range and were reported as treatment emerged AEs. In total, 162 deviations in 90 patients were outside extended ranges and therefore qualifying for AEs: 44 in 27 patients treated with 1x10 mg VAC BNO 1095, 65 in 33 patients treated with 2x10 mg VAC BNO 1095 and 53 in 30 Placebo treated patients. Increased basophil count was the most common clinically relevant deviation in blood parameters, followed by decreased neutrophil count, decreased blood bilirubin, decreased platelet count, decreased mean corpuscular haemoglobin concentration, increased mean corpuscular volume and increased monocyte count. The frequency of these deviations was comparable between the treatment groups.

More than 2 changes from normal to outside the extended normal range during the course of the study were observed in 5 patients treated with 1x10 mg VAC BNO 1095, 11 patients treated with 2x10 mg VAC BNO 1095 and 4 Placebo treated patients.

Each 5 blood parameters were clinically relevantly changed during the course of the study in Pat. No.°16 (i.e. increased INR, increased PTT, increased PTT ratio, increased neutrophil count, decreased total bilirubin) and Pat. No. 20 (i.e. increased INR, increased PTT, increased PTT ratio, increased WBC, increased basophil count) under

2x10 mg VAC BNO 1095 treatment and Pat. No. 277 with diagnosed thalassemia (i.e. decreased MCHC, increased monocyte count, decreased neutrophil count, increased potassium, increased total bilirubin) under Placebo treatment.

Vital signs

There were small and not clinically relevant changes from Baseline to end of treatment phase in average systolic and diastolic blood pressure and pulse rate.

The comparison between Placebo and the VAC BNO 1095 treatment showed no significant differences in the change of vital signs from Baseline after daily treatment with 1x10 mg and 2x10 mg.

Physical examination

No abnormal observations during the physical examinations including breast were made at the end of treatment phase.

Tolerability of treatment assessed by patient and investigator

The treatment tolerability was mainly assessed as 'good' and 'very good' by both patient and investigator. 'Moderate' tolerability was assessed by patient and investigator for about 5% of patients. None of them judged the treatment tolerability as 'very poor'. 'Poor' tolerability was assessed by investigator for two patients of the Placebo treatment only.

The pairwise comparisons between treatment groups showed a significantly statistical difference in tolerability comparing 2x10 mg VAC BNO 1095 vs. Placebo treatment assessed by patient (p=0.0450) and investigator (p=0.0186) in favour of 2x10 mg VAC BNO 1095. The comparison of 1x10 mg VAC BNO 1095 and Placebo treatment showed no statistical differences for assessed tolerability.

Conclusion:

The efficacy of treatment could not be proven because of Bionorica SE's decision not to perform any efficacy evaluations due to serious doubt in the general validity and credibility of data raised. Therefore the aim of the study to identify the optimal dosage of VAC BNO 1095 FCT for treatment of cyclic mastodynia and premenstrual syndrome could not be reached.

However, the treatment with VAC BNO 1095 (1x10 mg and 2x10 mg per day) compared with Placebo in women with cyclic mastodynia and PMS resulted in a favourable safety profile. Treatment with VAC BNO 1095 at daily doses up 2x10 mg VAC BNO 1095 for 3 treatment cycles was shown to be safe and well tolerated.
Therefore, the study should be repeated to prove the efficacy of VAC BNO 1095 FCT in the treatment of cyclic mastodynia and PMS.

Date of Report:

09 SEP 2013, Final Version 1.0