VIPOS - Visanne Post-approval Observational Study

International Active Surveillance Study of Women Taking Dienogest for Endometriosis

STUDY PROTOCOL

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ABBREVIATIONS

Abbreviation	Definition
AMI	Acute Myocardial Infarction
AT	As Treated
ATE	Arterial Thromboembolism
BMI	Body Mass Index
COC	Combined Oral Contraceptive
CVA	Cerebrovascular Accident
DNG	Dienogest
DVT	Deep Venous Thrombosis
EURAS	European Active Surveillance Study
FU	Follow-Up
GnRH	Gonadotropin-releasing hormone
HR	Hazard Ratio
INAS	International Active Surveillance (study)
ITT	Intention To Treat
LA	Leuprolide acetate
MPA	Medroxyprogesterone acetate
PASS	Post-Authorization Safety Study
PE	Pulmonary Embolism
SAE	Serious Adverse Event
SMAC	Safety Monitoring and Advisory Council
VIPOS	Visanne Post-approval Observational Study
VTE	Venous Thromboembolism
WY	Women-years
ZEG	Berlin Center for Epidemiology & Health Research (acronym for the German term ‘Zentrum für Epidemiologie & Gesundheits-forschung Berlin’)

1. INTRODUCTION

Endometriosis is a common, chronic, gynecological disease characterized by pain and impaired fertility. Prevalence estimates vary widely, however, the proportion of premenopausal women living with endometriosis is thought to be approximately 10% [1]. Endometriosis causes chronic inflammation, ovarian cyst formation, fibrosis and adhesions [1]. There seems to be little correlation between the extent of the disease and severity of pain experienced [2]. However, symptoms seem to respond to decreased circulating estrogen [3] and the mainstay of medical treatment is hormonal induced anovulation and a reduction in endogenous estrogen production.

While currently approved medications for endometriosis have proven to be effective in decreasing pelvic pain, many have clinically relevant side-effects. Danazol, a testosterone analogue, can cause androgenization and GnRH agonists are known to decrease bone mineral density. Consequently, treatment for endometriosis with these medications needs to be stopped after 6-12 months. Post-treatment endometrial lesions tend to regenerate, with many women's symptoms reoccurring 1-2 months after the cessation of treatment.

Dienogest (DNG) is a 19-nortestosterone derivative progestogen that is highly selective for progesterone receptors [4]. DNG has been available as part of a low-dose combined oral contraceptive containing 2mg of dienogest and 30µg of ethinylestradiol (DNG/EE) in Germany since 1995. As a progestin in DNG/EE, DNG is known for having strong endometrial effects that improve dysmenorrhea and decrease the duration of menstrual bleeding [5]. In addition, progestogens may also modulate pain associated with endometriosis by dampening neuronal activity [3]. As a monotherapy for the treatment of endometriosis DNG 2mg/day has been available in Japan since 2008. In Japan it has been found to be a reliable and effective treatment for dysmenorrhea, premenstrual pain, dyspareunia and diffuse pelvic pain associated with endometriosis [6]. Clinical trials in Europe have shown 2mg/day DNG to be effective in decreasing endometriosis associated pelvic pain with improved tolerability compared with 3.75mg leuprolide acetate (LA) [7-8]. Unlike LA, DNG has minimal effects on bone density and may offer women a new option for the long-term control of endometriosis symptoms.

A well-known class effect of progestogens is the induction of bleeding disturbances. 72% of women reported inter-menstrual spotting or bleeding as a side-effect of DNG use in a 52-week open-label study in Japan [9]. Metorrhagia symptoms tended to decrease towards the end of this trial and consequently it is not known what influence DNG will have on bleeding disturbances associated with endometriosis over a longer time frame. Given the initial increased incidence of metorrhagia in the Japan study and the overall increased risk of menorrhagia in women with endometriosis, a study assessing the incidence of anemia induced by bleeding disturbances in women receiving medical treatment for endometriosis is needed.

An ongoing concern associated with progestogens has been their potential role in influencing mood disturbances and, in particular, exacerbating depressive symptoms. In 2004, the European Health Authorities requested a desk review of newly diagnosed depression cases from the EURAS-OC study and found no increased risk for women using oral contraceptives compared to non-users [10]. Despite this reassurance, concerns remain. In addition, women who suffer from endometriosis are at high risk of developing depressive symptoms. Sepulcri et al assessed depressive symptoms amongst women with a surgical diagnosis of endometriosis and found 86.5% met SF-36 diagnostic criteria for depression, with 32.7% of women meeting the criteria for a severe depressive disorder [11]. Depressive symptoms may be correlated with the degree of chronic pelvic pain associated with the disease. Lorençatto found depressive symptoms in 86% of women with chronic pelvic pain associated with endometriosis while only 38% of women without pelvic pain met the diagnostic criteria for depression [12]. The complexities and potential interaction between depression, endometriosis and progestogens make it difficult to differentiate whether an individual's depressive symptoms are causally associated with progestin use or sequela of the disease process. Consequently, a population-based post-authorization safety study is needed to assess the potential influence of DNG on mood disturbance and depression in endometriosis patients.

To further investigate the impact that DNG will have on bleeding and mood disturbances associated with endometriosis, a non-interventional post-authorization safety study (PASS) is planned to investigate the safety of this medication for endometriosis with regard to medical interventions for anemia and worsening of depressive symptoms associated with the disease. The VIPOS study is part of a post-authorization safety and risk minimization commitment by Bayer Schering Pharmaceuticals. It will have a similar study design to the EURAS study design. The EURAS study design has now been used in several post-authorization safety studies including EURAS-HRT [13], EURAS-IUD, INAS-OC and INAS-SCORE. It has been clearly demonstrated that a large, prospective, controlled, non-interventional, long-term cohort study is suitable for

1. Safety monitoring of hormonal preparations
2. Reliable identification of relevant clinical outcomes and
3. Providing robust estimates of their incidence.

The procedures for recruitment, informed consent and follow-up have been modified slightly to comply with European regulations, and to ensure good recruitment rates and low loss to follow-up. The study should provide early information and regular updates on relevant clinical outcomes, which will contribute to a continuous risk - benefit assessment during long-term follow up (up to 6 years).

2. STUDY OBJECTIVES

The primary objective of the study is to assess safety aspects of Dienogest 2 mg/day (Visanne®) used as endometriosis therapy and of other approved hormonal treatments for endometriosis in a study population that is representative for the actual users of the individual preparations. This includes an estimate of the absolute risk of rare serious adverse outcomes.

The main clinical outcomes of interest for the short and long-term follow-up are:

- Medical intervention for clinically symptomatic anemia induced by cyclical bleeding disturbances (anemia)[1]
- First time occurrence of clinically relevant depression, or worsening of existing depression
- To analyze discontinuation patterns of DNG and other approved endometriosis treatments due to treatment failure (e.g. re-occurrence of pain, adverse drug reaction)

Secondary objectives are:

- To characterize the baseline risk of users of hormonal treatments prescribed for endometriosis (lifetime history of co-morbidity, risk markers, co-medication, socio-demographic and lifestyle data).
- To analyze the drug utilization pattern of DNG and other prescribed endometriosis treatments in a study population that is representative for typical use of the individual preparations under routine medical conditions.
- To investigate risks of short and long-term use of DNG and other prescribed endometriosis treatments in young women below the age of 18 years.

3. STUDY DESIGN

This is a large, prospective, controlled, non-interventional, long-term cohort study which follows two cohorts, users of DNG and users of other hormonal medications prescribed for the treatment of endometriosis. There is significant heterogeneity between countries in the medications currently available for the treatment of endometriosis. The study population will comprise of women taking DNG, Danazol, GnRH agonists, progestogens and other hormonal medications used for the treatment of endometriosis. This will include preparations that are formally not approved for the treatment of endometriosis (e.g., combined oral contraceptives); i.e.,

[1] Anemia associated with excessive, prolonged or irregular bleeding, including but not necessarily limited to, menorrhagia and metorrhagia. For the purposes of this protocol, this will be referred to as “anemia” for the remainder of the document.

all women who receive a prescription of hormonal preparations for the treatment of endometriosis are enrolled.

This 'all-comer'[2] approach minimizes selection bias and causes the least amount of influence on prescribing practices. It is therefore considered appropriate for this non-interventional, observational study design.

The described principle of 'non-interference' will also be used to provide standardized, comprehensive, reliable information on endometriosis treatment patterns. In this study, regular, active contacts with the cohort members (active surveillance) should provide all necessary information on health-related events or changes in health status after a new treatment for endometriosis is prescribed.

There will be active contacts with all study participants at baseline, six monthly for the first year and annually from years 2 until end of study. By means of these contacts, almost all relevant clinical outcomes will be captured. All clinically relevant serious adverse events will be verified by ZEG through contact with the relevant physicians and by reviewing pertinent source documentation. People without formal medical training often misclassify adverse events (feeling 'down' as clinical depression, tiredness and pallor as anemia) even if modern diagnostic procedures or careful clinical examination do not provide any indication of the perceived event. This type of inaccuracy in patient reports therefore requires careful validation. A standard algorithm will be used to classify 'clinically relevant depression' and medically treated anemia as "confirmed" or "not confirmed". At the end of the study this classification will be verified by blinded independent adjudication (cf. Appendix 2).

4. STUDY CENTERS

Recruitment of the cohort members will be conducted via a network of approximately 1,000 physicians (study centers) managing women with a diagnosis of endometriosis. The combined cohort will include 25,000 women. Study centers will be selected for study participation if they treat women for endometriosis. This will include both highly-specialized endometriosis centers and generalist gynecologists. The study population will include both mild and severe cases of endometriosis.

The study will be implemented in several European countries including, but not necessarily limited to, Germany, Austria, France and Poland. The sequence for starting the study in individual countries will depend upon the sequence of Visanne launches. Study participants should undergo follow-up for 3-6 years.

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[2] i.e., 1) all patients who are new users of endometriosis medication - regardless of the type of hormonal medication - are eligible for enrollment if they give their informed consent and 2) the recruitment of patients should not (significantly) influence the physician's prescribing behavior.

Study measures should not interfere with the prescribing behavior of physicians or with the individual needs of the participating women. The physician does not receive any incentive or reimbursement for prescribing a particular medication, nor does s/he receive any information that might influence the treatment information. In addition, significant efforts are to be undertaken to ensure standardized, comprehensive and reliable documentation of all baseline characteristics and adverse events during the follow-up period.

5. STUDY PARTICIPANTS

The study participants are women who

- are users of a newly prescribed regimen for endometriosis (starters, restarters or switchers)[3]
- are willing to participate in this long-term follow-up study

There are no specific medical inclusion or exclusion criteria. However, women

- who are not cooperative/available for follow-up may be excluded from study participation
- with a language barrier that prevents understanding of the questionnaires

At the participating centers, all women prescribed a new treatment for endometriosis are to be asked by their physician if they are willing to participate. As this is a non-interventional study, the possibility to participate in the study should not be discussed with the patient before both - physician and patient - agree upon the prescription. The physician is to explain the nature of the study, its purpose and associated procedures, and the expected duration of follow-up for each woman prior to her study entry. Each woman is to have ample opportunity to ask questions and must be informed about her right to withdraw from the study at any time without disadvantage and without having to provide reasons for her decision. This information will be provided on an informed consent and data privacy form which must be signed by all study participants. These documents are to be approved by the relevant local Ethics Committees and the relevant Data Privacy Office, if applicable.

Once enrolled, a subject may discontinue use of the relevant medication at any time. However, subjects will continue to be followed whether or not they remain on their treatment for endometriosis, provided that they do not withdraw their consent. During

[3] Starters are women who use a hormonal medication for the treatment of endometriosis for the first-time in their life. Restarters are women who restart the use of the previously used hormonal medication after an intake break of at least 4 weeks. Switchers are women who switch from one hormonal medication to another hormonal medication; use of the latter medication may start after an intake break or immediately after stop of the previous medication.

the follow-up phase, subjects will be asked whether they have discontinued their treatment or whether they have switched to another medication or received surgical treatment to manage their endometriosis. Information on the date and reason for discontinuation or switching during the follow-up phase will also be collected.

6. BASELINE SURVEY

Each physician's office will be provided with simple case report forms (questionnaires) for collecting data at baseline. The baseline visit will take place at the participating physician's office. All women who receive a new prescription for the treatment of endometriosis are to be asked if they are willing to participate. Only after the endometriosis medication has been prescribed will the physician discuss the study with the subject. This ensures that participation in the study is not considered a requirement for treatment. After discussing the study details (including follow-up procedures and intervals, content and duration of follow-up contacts, use of data collected, etc.), each subject will be asked to provide written informed consent to participate in the study. If the subject needs time to consider participation, she will be permitted to leave the physician's office with her prescription and take an appropriate period to decide whether to participate.

The informed consent will include permission for study data to be collected and analyzed and for contact to be made by the study team during the follow-up phase for collection of study information. Each subject will also be asked to provide information regarding alternative contacts (a close relative or friend, or primary care physician) if the study team cannot reach the subject after several attempts. Permission for the study team to contact a subject's primary care physician/ attending physician(s) and to review relevant source data (e.g., medical reports for validation of reported serious clinical outcomes) will also be sought. Follow-up frequency by the study team will be explained, and the content of follow-up contacts will be described.

Confidentiality will be maintained throughout the study and no personal information will be shared with alternative contacts. The funder - Bayer Schering Pharma AG - will not have access to names, addresses, or alternative contact information for the subjects and all individual subject data will remain anonymous. Personal and medical information will be recorded on separate documents. ZEG will ensure that access to personal information is restricted in accordance with data privacy rules.

Baseline data will be recorded in the physician's office on a questionnaire containing queries relating to the participant's state of health and potential risk factors. Demographic data, medical and gynecological history, detailed history of previous treatments for endometriosis, anemia and psychiatric illnesses, medication history and family history of depression and anemia/hematological problems as well as the addresses, e-mail addresses and phone numbers of the patient, relatives or friends, and the primary care physician are to be provided. In compliance with data protection

regulations names, addresses and phone numbers are to be documented on a separate sheet and stored separately in a locked cabinet.

7. FOLLOW-UP

A follow-up assessment for each woman is scheduled 6, 12, 24, 36 and depending on the date of enrollment 48, 60 and 72 months after baseline. Women will be followed-up for at least 3 years. Women recruited in the early phase of the study will be followed-up until study endpoint [max. 6 years].

Follow-up questionnaires will be mailed to the participating women, who often know more about potentially relevant health issues than the physician who made the initial prescription. This is especially true for potential adverse events treated by other physicians. Occasionally, events may be reported by the participant or by a participant's relatives, friends or attending physicians between the regular follow-ups. These reports will be documented and validated in the same way as regular reports (see section 8).

The follow-up questionnaires will address the occurrence of adverse events, changes in endometriosis treatment, use of concomitant medication, pregnancies and the change of potential risk factors. If the woman reports a change in treatment, reasons for switching to another endometriosis treatment or discontinuation of treatment will be requested. In case the regimen was changed or stopped due to a wish to conceive, or due to unintended pregnancy, a follow-up questionnaire requesting data on pregnancy related outcomes (abortions, stillbirths and congenital abnormalities) will be sent to the study participant.

A low "loss to follow-up rate" will be essential for the validity of the study. In order to minimize loss to follow-up a multi-faceted, four-level follow-up process will be established. Level 1 activities include mailing of the follow-up questionnaire and – in case of no response – reminder letter(s). If level 1 activities do not lead to a response, multiple attempts are to be made to contact the woman, friends, relatives and the gynecologist/primary care physician per phone. In parallel to these level 2 activities searches in national and international telephone and e-mail address directories are started (level 3 activities). If this is not successful, an official address search via the respective governmental administration will be conducted. This level 4 activity can provide information on new addresses, emigration or death. If necessary, a search in the national death registers is started at the end of the study to clarify the vital status of patients who are lost to follow-up after level 4 activities. Specific follow-up procedures will be governed by local peculiarities. Overall, the loss to follow-up of the combined cohort should be kept at less than 5%.

8. VALIDATION OF SELF-REPORTED EVENTS

A self-administered questionnaire used by study participants is a very sensitive tool which captures almost all serious clinical outcomes. From a methodological point of view, it captures a much higher proportion of relevant outcomes than methods relying on events reporting by the prescribing physician (e.g. gynecologist). However, laypersons can misinterpret diagnostic treatments leading to a significant difference between the number of events reported and the number that are validated and confirmed by the ZEG team. Therefore, validation of the self-reported events is of utmost importance.

Validation of self-reported events begins at the level of the national field organization with a review of all subjective "events." Potential serious outcomes are reported to ZEG on a continuing basis and validated by ZEG.

If an event is reported by a woman, the woman's symptoms and signs of disease and, if possible, the diagnosis as perceived by the patient is recorded. The name and address of the relevant physician (attending physician, physician responsible for the follow-up treatment on discharge from hospital or primary care physician) should be provided by the participant. The validation team will ensure that informed consent to access the participant's medical records is "re-established" and that the participant is aware of her rights regarding confidentiality and study participation.

Follow-up questionnaires containing information on such an event are immediately passed on to the Medical Review group at ZEG. If information is unclear or missing, the woman will be contacted via phone, e-mail or other means. For many serious outcomes it will be necessary to contact the diagnosing and/or treating physician for clarification and validation of the information received from the patient. This procedure is mandatory for all serious clinical outcomes (incl. anemia and depression).

Under routine medical conditions, diagnosis of an SAE is not always confirmed by a diagnostic method with high specificity. Therefore, SAEs are classified by the investigators as "confirmed" or "not confirmed" according to a predefined algorithm (cf. Appendix 1).

In order to minimize classification bias - particularly if it selectively affects an individual exposure cohort - classification of self-reported serious events into confirmed and not confirmed cases will be adjudicated by two blinded medical boards. The 'Hematology Board' consists of three independent medical experts specialized in internal medicine/hematology and gynecology. The 'Depressive Illness Board' consists of three specialists in psychiatry/psychological medicine. Blinded adjudication of both anemia and depressive illnesses are scheduled at the conclusion of the study (Beginning of 2017). The Safety Monitoring and Advisory Council (see section 13) will appoint these experts who will review all available information on the reported anemia and depression cases. Brand names, dose, regimen and

composition of the endometriosis medication used by the reporting woman will be rendered anonymous. The adjudicators will perform the review independently of each other and without knowing the judgment of the other adjudicators. A conservative approach will be used for the blinded adjudication with cases classified as "confirmed" if at least one adjudicator classifies a report as a confirmed case of anemia or depression. More details on the blinded adjudication procedure are given in Appendix 2.

9. REPORTING OF SERIOUS AND/OR UNEXPECTED ADVERSE EVENTS

ZEG will report all serious[4] and/or unexpected events that are possibly related to the use of any endometriosis treatment to the relevant pharmaceutical companies. A physician on the ZEG study team will assess the likelihood of a causal relationship to the medication use for each serious adverse event in accordance with a predefined algorithm (cf. Appendix 3). Overall, the handling of adverse events will follow Volume 9A of 'The Rules Governing Medicinal Products in the European Union (part I, section 7).

ZEG will not monitor whether the pharmaceutical companies meet their obligation to report these events to the Health Authorities according to (inter)national rules.

10. DATA MANAGEMENT

When questionnaires are received from study participants, all pages are counted and the questionnaire is date-stamped. Questionnaires are to be checked for correct subject identification number, missing pages, legibility, and incomplete information on the questionnaires (cf. section 6 'Baseline survey' and 7 'Follow-Up'). Missing pages, illegible or missing information are requested from the study participants prior to data entry of the respective questionnaire.

Data are entered by double data entry via formatted entry screens designed to reflect the appearance of the questionnaire. Discrepancies between first and second data entry are identified by comparison of the two entry files within the statistical software SAS. The decision on the true entry is done by the responsible data manager at ZEG. This may require direct contact with the study participant who filled in the questionnaire. Corrections will be made to the questionnaire only after contact with the study participant or her treating physician (cf. section 8 'Validation of Self-Reported Events'). All corrections are dated and initialed by the data manager who received the relevant new information (e.g., via direct contact or by a copy of medical reports/documents). The incorrect CRF entry will be crossed out; however, it must

[4] Serious adverse event means any adverse event that results in death, a life-threatening experience, inpatient hospitalization, persistent or significant disability/incapacity, or requires medical/surgical intervention to prevent one of said outcomes.

remain legible, and the correct entry will be placed next to it. The reason for any correction of medical data on the questionnaire must be documented.

Quality control of entered data will be supported by SAS plausibility programs which include range, coding, missing and date checks as well as cross-reference (consistency) checks between variables.

11. DATA ANALYSES

Three primary outcomes of interest, anemia, depression and treatment failure[5], will be analyzed for inferential statistics using Cox regression analysis. Bonferroni-Holm correction will be used to account for multiple testing.

Based on available data and pharmacological/pharmacokinetic considerations the *a priori* assumption is that use of DNG is not associated with an increased risk of anemia compared to other approved endometriosis medications. Therefore, a non-inferiority design to investigate the anemia risk of DNG had been chosen. The analysis will be based on the comparison of the upper confidence limit for the point estimate of the anemia hazard ratio with the predefined non-inferiority margin (cf. section 12).

The null hypothesis to be tested is: $\mathbf{HR}_{\text{anemia}} \geq \mathbf{2}$ (i.e., the anemia hazard ratio for DNG vs. other approved endometriosis medications is higher or equal to 2). The alternative hypotheses are: $\mathbf{HR}_{\text{anemia}} < \mathbf{2}$.

For clinically relevant depression (first episode or worsening), the *a priori* assumption is that use of DNG is not associated with an increased risk of depression compared to other approved endometriosis medications. A non-inferiority design has been chosen, with primary analysis based on the comparison of the upper confidence limit for the point estimate of the depression hazard ratio with the predefined non-inferiority limit (cf. section 12).

The null hypothesis to be tested is: $\mathbf{HR}_{\text{depression}} \geq \mathbf{2}$ (i.e., the depression hazard ratio for DNG vs. other approved endometriosis medications is higher or equal to 2). The alternative hypothesis is: $\mathbf{HR}_{\text{depression}} < \mathbf{2}$.

There are both pharmacological and clinical indications that suggest that DNG may be superior to other approved endometriosis medications as a long-term treatment for endometriosis. That is, a statistical comparison of DNG vs. other approved

[5] 'Treatment failure is defined as cessation of treatment caused by lack of efficacy, loss of efficacy or an adverse drug reaction and does not include women who stop treatment after pre-defined treatment periods (eg. after six months for GnRH agonists).

endometriosis medications may show a difference in 'treatment failure', with DNG users continuing on treatment for longer periods of time. 'Treatment failure is defined as cessation of treatment caused by lack of efficacy, loss of efficacy or an adverse drug reaction and does not include women who stop treatment after pre-defined treatment periods (e.g., after six months for GnRH agonists). A superiority design to investigate 'treatment failure' for DNG has been chosen. The analysis will be based on a 5% point difference (difference of 0.05) of DNG vs. other approved endometriosis medications.

Safety monitoring during study conduct will be based primarily on the ITT analysis of crude data. The final analyses will include both an "as treated" (AT) and an intention-to-treat (ITT) analysis using Cox regression models. The safety conclusions of the study, however, will be based on the AT analyses because the ITT approach potentially dilutes differences between treatments.

Crude as well as adjusted hazard ratios will be calculated. The appropriate confounding variables will be built into the statistical model. Based on the expectation of a small absolute number of serious outcomes of interest the number of confounding variables will be limited to established risk factors for these outcomes. For anemia these will include age, duration of current use, and family history of bleeding disorders and a past history of anemia. For depression, age, chronic pelvic pain, anxiety disorder and a family history of depression are proposed. For 'treatment failure' chronic pelvic pain, age and previous surgical treatment will be included. The final decision on the confounding variables will be made by the Safety Monitoring and Advisory Council before the first interim analysis of follow-up data. In addition, alternative analysis will be performed with other potential baseline risks to check the appropriateness of this decision.

During the interim analysis, baseline characteristics of cohorts will be summarized and crude data analyzed for the primary outcomes of interest. The results will be reported to the Safety Monitoring and Advisory Council (SMAC) for safety monitoring.

A detailed statistical analysis plan will be developed by the Principal Investigator during the first year after study start. The final analysis plan will be approved by the Safety Monitoring and Advisory Council before the first interim analysis of follow-up data.

Biannual interim reports will be provided to the funder following release of the interim analyses results by the independent Safety Monitoring and Advisory Council (cf. section 13).

12. SIZE OF THE STUDY AND EVALUTION

The 3 to 6 year follow-up of 25,000 women should result in approximately 89,000 documented women-years. This estimate is based on the assumptions that (1) ZEG's physicians' network could recruit 25,000 women within three years, and (2) the annual drop-out rate is 10% (based on the EURAS-OC [1] and LASS studies). Details are provided in Table 1 and are based on the assumption that the follow-up period is a maximum of 6 years.

Table 1: Expected observation time (max. 6 years follow-up): Patient recruitment within 3 years (annual recruitment rate = 8,334 women)

	Sub-cohorts recruited during the					
Time (y)*	**1st study year**		**2nd study year**		**3rd study year**	
	No. of women	Time of observation	No. of women	Time of observation	No. of women	Time of observation
1	7,910	4,035				
2	7,119	7,515	7,910	4,035		
3	6,407	6,763	7,119	7,515	7,910	4,035
4	5,766	6,087	6,407	6,763	7,119	7,515
5	5,190	5,478	5,766	6,087	6,407	6,763
6	4,671	4,930	5,190	5,478	5,766	6,087
WY (total)		34,808		29,878		24,400
WY (grand total)	89,086					

* Time after start of recruitment

** The number of recruited women equals 8,334. However, the number of women at the end of the first year is lower because some women will drop out during the first year (daily drop-out rate is ~ 0.029%).

The study was designed to analyze rare events (according to the CIOMS classification 1 – 10 and less than 1 event(s) per 10,000 women-years, respectively). The adverse events of particular interest for the sample size calculations are anemia, clinically relevant depression and treatment failure.

The background prevalence of anemia in premenopausal European women is approximately 10-15% [14]. Based on this high prevalence and the fluctuating character of the disease the investigators anticipate an incidence of new or recurrent anemia in an active surveillance study of 0.01-0.02. The sample size calculation is based on a conservative estimate of 0.01 (or 1 event per 100 WY).

A conservative estimate of the prevalence rate for depression in women with endometriosis is 20%. This figure is based on a systematic literature review of the available evidence and an analysis of EURAS/INAS results [10-12]. For newly diagnosed or worsening depression the expected incidence rate is at least 0.01. Based on this incidence, the sample size outlined below was calculated; in case the

study shows other incidence rates at a later point in time, a re-calculation may be necessary and will be discussed with the Safety Monitoring and Advisory Council if required.

Based on the natural history of endometriosis treatment, we anticipate that the majority of women will stop or change treatment regimes during the course of this study. We expect an incidence rate of women ceasing or changing treatment ('treatment failure') for other approved endometriosis medications due to lack of efficacy, loss of efficacy or an adverse drug reaction of at least 0.3. For the DNG cohort a proportion of 0.25 of the total study population seems to be realistic.

Overall, 3 hypotheses will be tested (cf. section 11). The problem of multiple comparisons is addressed by using the Bonferroni-Holm correction to maintain the overall error rate. For the calculation of the sample sizes a statistical significance level of 1/3 times what it would be if only one hypothesis were tested (i.e., the individual tests will be based on an α level of 0.0167 instead of 0.05) is used.

Power calculations based on the incidences given above showed that approximately 84,000 women-years would be needed to show non-inferiority of DNG versus other approved endometriosis medications for anemia. The calculations for anemia are based on the assumptions given in Table 2. In essence, the study is powered to exclude a two-fold risk of anemia for the DNG with at least 10% of the total exposure – if the true risk of anemia is not different for the relevant sub-cohorts.

Furthermore, 84,000 WY would be sufficient to also exclude a two-fold risk of clinically relevant depression (cf. Table 3), assuming that DNG and the reference cohorts account for at least 10% and 5% of the total exposure, respectively.

For 'treatment failure' approximately 29,500WY will be required to show that DNG is superior to other approved endometriosis medications (cf. Table 4), assuming that the proportion of DNG users is 10% and the users of the reference cohort account for 5% of the total exposure.

Table 2: Power calculation[15] for anemia based on the assumption that the true incidence of DNG cohort is not different from other approved endometriosis medications (reference cohort)

Test significance level, α (one-sided)	0.0083 (= 0.0167 two-sided)
Anemia Incidence for reference cohort	0.01
Non-inferiority margin	0.01 (equal to the anemia incidence for the reference cohort)
Expected anemia incidence for DNG cohort	0.01
Power (%)	90
Proportion of DNG users (% of study population)	10
Proportion of reference users (% of study population)	5
Required women years in DNG cohort	8,400
Required women years in reference cohort	4,200
Total women years	84,000

Table 3: Power calculation[15] for depression based on the assumption that the true incidence in the DNG cohort is not different from other approved endometriosis medications (reference cohort).

Test significance level, α (one-sided)	0.0083 (= 0.0167 two-sided)
Depression Incidence for reference cohort	0.01
Non-inferiority margin	0.01 (equal to the depression incidence for the reference cohort)
Expected depression incidence for DNG cohort	0.01
Power (%)	90
Proportion of DNG users (% of study population)	10
Proportion of reference users (% of study population)	5
Required women years in DNG cohort	8,400
Required women years in reference cohort	4,200
Total women years	84,000

Table 4: Power calculation[15] for 'treatment failure' based on the assumption that the true incidence in the DNG cohort is ~ 2,500/10,000 compared to ~ 3,000/10,000 in users of other approved endometriosis medications (reference cohort).

Test significance level, α (two-sided)	0.0167
Incidence of treatment failure for reference cohort	0.30
Clinically relevant difference	0.05
Expected incidence of treatment failure for DNG cohort	0.25
Power (%)	90
Proportion of DNG users (% of study population)	10
Proportion of reference users (% of study population)	5
Required women years in DNG cohort	2,950
Required women years in reference cohort	1,475
Total women years	29,500

These power calculations suggest that this study is sufficiently powered to show non-inferiority of DNG compared to other approved endometriosis medications with regard to anemia and clinically relevant depression, as well as superiority with regards to 'treatment failure'. However, exact power calculations based on actual incidences and drop-out rates should be done on the basis of two years follow-up data. If these calculations do not confirm the assumed incidences and drop-out rates, the independent Safety Monitoring and Advisory Council (SMAC) may discuss the need for adapting patient numbers and follow-up times.

13. SAFETY MONITORING AND ADVISORY COUNCIL

This study will maintain scientific independence and will be governed by an independent Safety Monitoring and Advisory Council (SMAC). Bayer Schering Pharma AG Berlin will provide an unconditional grant. The Berlin Center for Epidemiology and Health Research (ZEG), Germany and its research team will be accountable to SMAC in all scientific matters.

The SMAC members will be international experts in relevant scientific fields (e.g., epidemiology, gynecology, psychiatry and internal medicine. The members will receive remuneration of expenses and an honorarium to compensate for loss of potential earnings during their work for SMAC. The members will not be involved in or paid for the operational conduct of the study.

14. STUDY MANAGEMENT

This study will be conducted in accordance with

- 'Guidelines for Good Pharmacoepidemiology Practices (GPP)' issued by the International Society for Pharmacoepidemiology in 2007
- 'Good Epidemiological Practice (GEP) – Proper Conduct in Epidemiologic Research' issued by the International Epidemiological Association (IEA) European Federation in 2007
- ENCePP code of conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies, 2010
- The ethical principles that have their origin in the Declaration of Helsinki.

15. ETHICS AND PRIVACY

The study will only start after all relevant legal, administrative and ethical requirements (including all requirements regarding the enrollment of minors) have been fulfilled. Information on the identity of the patients and treating physicians will be kept separated from the clinical information throughout the study. All relevant national data protection laws will be followed. The study protocol will be submitted to the relevant Ethics Committees, Institutional Review Boards and regulatory authorities for comments and approval.

Subjects will sign informed consent forms at baseline after reading a subject information sheet and discussing the study with the participating physician. The physician will describe the purpose of the study, the non-interventional character of the study, timing and expected content of follow-up phase contacts, and collection of alternative contact information. Consent will include permission to contact any treating physician to follow up on specific safety outcomes. Subjects will be informed that ZEG's study team will contact them during the follow-up phase to ask a predefined set of safety related questions or to update alternative contact information. Answers to these questions will remain anonymous when forwarded to Bayer Schering Pharma AG or the Safety Monitoring and Advisory Council.

Subjects will be asked to provide personal contact information (e.g., telephone number, home and e-mail address) and information regarding alternative contacts (e.g., relative, friend, general practitioner) in case they cannot be reached. In the event that a subject cannot be reached during the follow-up phase, local organizations will attempt to reach an alternative contact to re-establish contact with the subject. Subjects may be contacted between two follow-up points to confirm that their personal contact information is correct.

Subjects retain the right to withdraw their consent at any time during the study.

16. STUDY FEASIBILITY

ZEG's study team has performed large, multi-national, observational studies on pharmacoepidemiological issues for more than 30 years – in particular in the area of women's health care. Many of these studies have prospectively followed-up patients for 5-10 years. In addition ZEG developed the EURAS/INAS study design. ZEG has established a broad network of several thousands gynecologists in Europe who are currently recruiting women for INAS-like studies. With this established international network no major problems are expected for the recruitment of study participants. Furthermore, the drop-out and follow-up rates presented in this study protocol are based on comprehensive experience from similar studies. Therefore the conduct of the VIPOS study according to this study protocol has a high probability of success.

17. MILESTONES

Precise recruitment and follow-up milestones will depend on the specific launch dates of Visanne in Europe. However, we anticipate the first patient to be recruited in November 2010. The first Safety and Medical Advisory Council (SMAC) will take place in the second quarter of 2011, and 6-monthly thereafter, unless otherwise agreed upon by SMAC members. Written reports up-dating regulatory authorities of the study progress and important SMAC decisions will follow these meetings. The final evaluation and analysis of anemia and depression (with blinded adjudication) will take place at the conclusion of the study follow-up period. A comprehensive study report will be made available after the completion of the study.

18. PUBLICATIONS

The results of this study will be published. In accordance with the International Committee of Medical Journal Editors (ICMJE) initiative requiring prior entry of clinical studies in a public registry as a condition for publication, the study will be registered in the U.S. National Institutes of Health's protocol registration database (http://ClinicalTrials.gov).

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APPENDIX 1: VALIDATION OF SELF-REPORTED EVENTS

Anemia

- Definite Event:
  - Confirmed by repeated reliable laboratory test (e.g. hemoglobin, packed cell volume), plus pertinent therapy (blood or iron transfusion, iron tablets) and
  - Anemia is associated with prolonged, excessive or irregular bleeding
- Probable Event:
  - No reliable laboratory data available, but clinical diagnosis stated by a physician, followed by pertinent therapy (see above). and
  - Anemia is associated with prolonged, excessive or irregular bleeding
- Event not confirmed:
  - Diagnosis reported by the patient is excluded by diagnostic procedures
  - A different medical condition is diagnosed by the attending physician
  - The woman did not contact a health professional to clarify her symptoms and no diagnostic measures were performed that could have clarified the diagnosis

Definite and probable events will be classified as 'confirmed events'.

Clinically relevant Depression

- Definite Event:
  - Diagnosis is confirmed by a physician specialized in psychiatry using validated instruments (e.g. HAM-D, BECK depression inventory)
  - Confirmed suicide or attempted suicide in a participant with a past history of depression
- Probable Event:
  - Clinical diagnosis confirmed by physician specialized in psychiatry without the use of validated instruments (see above)
  - Confirmed (attempted) suicide without a previous psychiatric diagnosis
- Event not confirmed:
  - Diagnosis reported by the patient is excluded by diagnostic procedures
  - Diagnosis is confirmed by a physician without specialized training in psychiatric diseases
  - A different medical condition is diagnosed by the attending physician
  - The woman did not contact a health professional to clarify her symptoms and no diagnostic measures were performed that could have clarified the diagnosis

Definite and probable events will be classified as ‘confirmed events’.

Other Serious Adverse Events

- Definite Event:

  Diagnostic measures with high specificity (e.g., ultrasound diagnosis of VTE, ECG with typical ST segment elevation for acute myocardial infarction, histology for cancers, two-sided blood pressure measurement with diastolic blood pressure of more than 120 mmHG for hypertensive crisis)

- Probable Event:

  Absence of confirmation by a diagnostic measure with high specificity, but clinical diagnosis confirmed by a health professional or supported by diagnostic tests with low specificity (D-dimer for VTE, typical ECG/blood gas tests for PE or confirmation of diagnosis by the treating physician for cancer). These cases are usually characterized by a subsequent specific therapy (such as fibrinolysis, long-term anticoagulant therapy or chemotherapy/radiotherapy). However, if the attending physician confirms that the diagnosis is correct, the event will be classified as a probable event even if specific treatment was not given.

- Event not confirmed:
  - Diagnosis reported by the patient is excluded by diagnostic procedures
  - A different medical condition is diagnosed by the attending physician
  - The woman did not contact a health professional to clarify her symptoms and no diagnostic measures were performed that could have clarified the diagnosis

Definite and probable events will be classified as ‘confirmed events’.

APPENDIX 2: BLINDED ADJUDICATION

The following adjudication procedure will be established:

1) The three specialists will independently adjudicate the outcomes of interest
2) The individual assessments will be documented
3) The Individual assessments will be compared
4) Discussion of “split decisions” among the adjudicators without enforcement of a unanimous decision
5) Independent re-adjudication of the discussed cases by the individual adjudicators
6) Documentation of the individual assessments

Based on this procedure four different classification strategies will be possible

I. Classification of the reported event according to the assessment of the majority of adjudicators before the discussion of “split decisions” takes place (i.e., “majority vote” based on step 2 of the six-step procedure described above)

II. Classification of the reported event according to the assessment of the majority of adjudicators after discussion of “split decisions” takes place (i.e., majority classification based on step 6 of the six step procedure described above)

III. Classification of the reported event as confirmed if at least one adjudicator had classified the event as confirmed before the discussion of split decisions took place (i.e., “worst case decision” based on step 2 of the six-step procedure described above)

IV. Classification of the reported event as confirmed if at least one adjudicator had classified the event as confirmed after the discussion of split decisions took place (i.e., “worst case decision” based on step 6 of the six-step procedure described above)

The final analysis will be based on strategy III (worst case decision without discussion of split decisions) because it represents the most conservative approach. Alternative analyses will be possible on request of the Safety Monitoring and Advisory Council or regulatory authorities.

APPENDIX 3: CAUSALITY ASSESSMENT

Categories (Code)	Definition
no (1)	The time course between administration of the study drug and occurrence or worsening of the adverse event rules out a causal relationship and/or another cause is confirmed and no indication of involvement of the study drug in the occurrence/worsening of the adverse event exists.
unlikely (2)	The time course between administration of the study drug and occurrence or worsening of the adverse event makes a causal relationship unlikely and/or the known effects of the study drug or of the substance class provide no indication of involvement in occurrence/worsening of the adverse event and another cause adequately explaining the adverse event is known and/or regarding the occurrence/worsening of the adverse event a plausible causal chain may be deduced from the known effects of the study drug or the substance class, but another cause is much more probable and/or another cause is confirmed and involvement of the study drug in the occurrence/worsening of the adverse event is unlikely.
possible (3)	Regarding the occurrence/worsening of the adverse event, a plausible causal chain may be deduced from the pharmacological properties of the study drug or the substance class, but another cause just as likely to be involved is also known or although the pharmacological properties of the study drug or the substance class provide no indication of involvement in the occurrence/worsening of the adverse event, no other cause gives adequate explanation.
probable (4)	The pharmacological properties of the study drug or of the substance class and/or the course of the adverse event after dechallenge and, if applicable, after rechallenge and/or specific tests (e.g. positive allergy test, antibodies against study drug/metabolites) suggest involvement of the study drug in the occurrence/worsening of the adverse event, although another cause cannot be ruled out.
definite (5)	The pharmacological properties of the study drug or of the substance class and the course of the adverse event after dechallenge and, if applicable, after rechallenge and specific tests (e.g. positive allergy test, antibodies against study drug/metabolites) indicate involvement of the study drug in the occurrence/worsening of the adverse event and no indication of other causes exists.