PASS information

Title	International Active Surveillance Study of Medication Used for the Treatment of Endometriosis: Visanne Post-approval Observation Study (VIPOS)
Version identifier of the final study report	2.0
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EU PAS register number	EUPAS 1613
Active substance	Dienogest
Medicinal product	Visanne 2mg
Product reference	*[Reference number(s) of centrally authorized products and/or, if possible, of nationally authorized products subject to the study]*
Procedure number	*[If applicable, Agency or national procedure number(s), e.g. EMA/X/X/XXX]*
Marketing authorization holder(s)	Bayer AG
Joint PASS	No
Research question and objectives	Assessment of safety of Dienogest 2 mg/day launched as endometriosis therapy in 2010 in comparison with other hormonal endometriosis drugs. Special focus on medical intervention for anemia associated with endometriosis-related bleeding, first time occurrence or worsening of existing clinically relevant depression, discontinuation patterns due to treatment failure
Country(-ies) of study	Germany, Poland, Russia, Hungary, Switzerland, and Ukraine
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1. Abstract

Title

International Active Surveillance Study of Medication Used for the Treatment of Endometriosis: Visanne Post-approval Observational Study (VIPOS)

Keywords

Endometriosis, Dienogest, Depression, Anemia, Treatment discontinuation

Rationale and background

Endometriosis is a chronic, gynecological condition characterized by pain and impaired fertility. Dienogest (DNG) 2 mg (Visanne) was approved for endometriosis treatment in 2010. The VIPOS study was part of the post-authorization safety and risk minimization commitment and was designed to assess the safety of DNG 2 mg in comparison to other hormonal treatments for endometriosis.

Research question and objectives

To investigate the incidence of the first-time occurrence or worsening of clinically relevant depression and anemia associated with endometriosis-related bleeding.

Study design

Large, prospective, non-interventional cohort study with active surveillance in six European countries. Women with a new hormonal therapy for endometriosis were enrolled by gynecologists and specialized centers between 2010 and mid-2016. Information was collected via self-administered questionnaires at study entry and during follow-up until October 2018. Follow-up questions included information on current health status and further use of endometriosis treatment.

Setting

Study participants were recruited via a network of health care professionals routinely prescribing medication to treat endometriosis (that is gynecologists) in Germany, Poland, Russia, Hungary, Switzerland, and Ukraine.

Subjects and study size, including dropouts

A total of 27,840 users of a new endometriosis treatment[1] were followed up for 86,277 women-years (WY). A total of 4,683 out of 27,840 women (16.8%) were lost to follow-up during the follow-up period.

[1] This study was designed as an "all-comer" study; study participants were eligible if prescribed a new medication for the treatment of their endometriosis on the day of recruitment. Medications prescribed included for example combined oral contraceptives, dienogest (Visanne), danazol and GnRH-a.

Variables and data sources

Primary statistical variables: Anemia HR for DNG vs. OAED adjusted for age, history of bleeding disorders and history of treated anemia. Depression HR for DNG vs. OAED adjusted for age, personal and family history of depression and prior use of an antidepressant. Treatment discontinuation due to treatment failure OR for DNG vs. OAED adjusted for age, personal and family history of depression and severity of endometriosis-related pain. Results are based on patient-reported anemia and depression that were validated via the attending physicians and medical records.

Results

The overall incidence rate of anemia was 23.4 per 10,000 WY (197 cases). The incidence rates per user cohort were as follows: DNG (33.5 per 10,000 WY; 15 cases); OAED (49.1 per 10,000 WY; 12 cases); NAED (22.9 per 10,000 WY; 92 cases); ex-users (21.2 per 10,000 WY; 78 cases). The adjusted HRs were 1.1 (95% CI 0.4-2.6) for DNG vs. OAED and 1.3 (95% CI, 0.7-2.4) for DNG vs. NAED.

There were 139 depression cases which resulted in overall incidence rates for new or worsening depression which were substantially lower than expected. The incidence rates per user cohort are as follows: DNG (35.7 per 10,000 WY; 16 cases); OAED (8.2 per 10,000 WY; 2 cases); NAED (17.0 per 10,000 WY; 68 cases); ex-users (14.4 per 10,000 WY; 53 cases). The adjusted hazard ratios were 1.8 (95% CI, 0.3 – 9.4) for DNG vs OAED and 1.5 (95% CI, 0.8 – 2.8) for DNG vs NAED.

From a total of 42,342 treatment starts, there were 4,733 observed treatment failures. This resulted in an overall incidence proportion (IP) of 11.2 per 100 treatment starts. The IPs per user cohort were as follows: DNG (IP = 16.1 per 100 starts; 668 treatment failures from 4,137 treatment starts;); OAED (IP = 5.1 per 100 starts; 203 treatment failures from 4,001 treatment starts); NAED (IP = 11.3 per 100 starts; 3,862 treatment failures from 34,204 treatment starts). Interpretation of these results is challenging due to differences in the indicated duration of use between (sub-)cohorts and in the administration methods (that is some methods, such as injectable three-month Depo, do not allow for immediate discontinuation by the patient).

In summary, the incidence rates for anemia, depression and treatment discontinuation differed between the DNG, OAED, and NAED (sub-)cohorts.

Discussion

In this study, the use of DNG, OAED, and NAED for the treatment of endometriosis was associated with differing risks of anemia, depression and treatment failure during routine clinical use. Overall the incidence rates of confirmed events for both anemia and depression were lower than anticipated. In addition, large inter-country variance in prescribed endometriosis treatment, the severity of reported endometriosis and incidence of reported anemia and depression cases makes comparisons across countries and (sub-)cohorts difficult and interpretation of these findings challenging.

Due to these limitations, the study was under-powered to detect two-fold increased risk anemia amongst DNG users compared to OAED and NAED users. However, we were able to exclude a three-fold increased risk.

An increased risk of worsening and of new-onset depression in DNG users compared to OAED users could not be excluded.

The study has also produced new insights into endometriosis symptoms and management across Europe that could not have been obtained through automated databases or claims databases. The investigator and the Safety Monitoring and Advisory Council have concluded that the INAS-VIPOS study results are valid within the general limitations of observational research and that no safety concern was identified for DNG.

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2. List of abbreviations

Abbreviation	Definition
ADB	Administrative Database
AMI	Acute Myocardial Infarction
AT	As Treated
ATE	Arterial Thromboembolism
BMI	Body Mass Index
CATI	Computer Assisted Telephone Interview
CAWI	Computer Assisted Web Interview
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CHC	Combined Hormonal Contraceptives
COC	Combined Oral Contraceptive
CVA	Cerebrovascular Accident
DIMDI	German Institute for Medical Documentation and Information (acronym for German term: Deutsche Institut für Medizinische Dokumentation und Information)
DNG	Dienogest
DVT	Deep Venous Thrombosis
EE	Ethinylestradiol
EMT	(Hormonal) Endometriosis Treatment
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EURAS	European Active Surveillance Study
FU	Follow-Up
GEP	Good Epidemiological Practice

GnRH-a	Gonadotropin-releasing Hormone agonists
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCP	Health Care Professional
HR	Hazard Ratio
ICD	International Classification of Diseases
INAS	International Active Surveillance (study)
IR	Incidence rate
ITT	Intention To Treat
MAWI	Mobile Assisted Web Interview
MEB	Medicines Evaluation Board
NAED	Non-Approved Endometriosis Drugs
OAED	Other Approved Endometriosis Drugs
OPS	Operation and Procedure coding list (acronym for German term: Operationen- und Prozedurenschlüssel)
OR	Odds ratio
PASS	Post-Authorization Safety Study
PE	Pulmonary Embolism
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDB	Study Database
SMAC	Safety Monitoring and Advisory Council
TIA	Transient Ischemic Attacks
UK	United Kingdom
USA	United States of America

VIPOS	Visanne Post-approval Observational Study
VTE	Venous Thromboembolism
WY	Women-years
ZEG	Berlin Center for Epidemiology and Health Research (acronym for the German term “Zentrum für Epidemiologie & Gesundheitsforschung Berlin”)

3. Investigators

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4. Other responsible parties

Not applicable

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Safety Monitoring and Advisory Council (SMAC):

[redacted]

Study conduct was overseen by an independent scientific committee. ZEG Berlin was accountable to the SMAC in all scientific matters. Members of the SMAC received remuneration of expenses and an honorarium to compensate for the loss of potential earnings during their work for SMAC. Over and above this, the members were not involved in the conduct of the study and did not receive any additional payments.

[2] [redacted]

5. Milestones

Milestone	Planned date	Actual date	Comments
Registration in the EU PAS register	QIV, 2010	27 OCT 2010	None
Date of Ethical approval in Germany	QIV, 2010	06 DEC 2010	None
Date of Ethical approval in Hungary	QI, 2011	08 MAR 2011	None
Date of Ethical approval in Switzerland		08 MAR 2012	None
Start of data collection	DEC 2010	DEC 2010	Start of patient recruitment
Recruitment completed (I)	DEC 2013	June 2014	Planned date was changed in order to reach the target of 25,000 study participants
Recruitment completed (II)		June 2016	Recruitment of additional >2,000 OAED patients completed
End of data collection	DEC 2016	31 OCT 2018	Last patient follow-up Change caused by prolongation and re-start of recruitment as well as prolongation of follow-up time (study protocol amendment SEP 2017, cf. Section 8)
Interim report 1	NOV 2011	30 JAN 2012	Originally planned dates of Interim Reports were slightly changed due to the meeting schedule of the Safety Monitoring and Advisory Council
Interim report 2	MAY 2012	15 JUN 2012	None
Interim report 3	NOV 2012	18 JAN 2013	None
Interim report 4	MAY 2013	28 JUN 2013	None
Interim report 5	NOV 2013	24 JAN 2014	None
Interim report 6	MAY 2014	24 JUL 2014	None
Interim report 7	NOV 2014	23 JAN 2015	None
Interim report 8	MAY 2015	06 AUG 2015	None
Interim report 9	NOV 2015	19 FEB 2016	None
Interim report 10	MAY 2016	30 AUG 2016	None
Interim report 11	NOV 2016	06 FEB 2017	None
Interim report 12	MAY 2017	17 AUG 2017	None
Interim report 13	NOV 2017	31 JAN 2018	None
Interim report 14	MAY 2018	13 AUG 2018	None
Final report of study results	JUN 2017	Q 1/2019	None
Final manuscript submitted	31 MAR 2019	?	

6. Rationale and background

Endometriosis is a common, chronic, gynecological disease characterized by pain and impaired fertility. While currently approved medications for endometriosis have proven to be effective in decreasing pelvic pain, many have clinically relevant side effects. Danazol, a testosterone analog, 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 six-12 months. Other hormonal preparations, such as combined oral contraceptives, are frequently prescribed in routine clinical practice to treat endometriosis, even though they have not been approved for this purpose.

Dienogest (DNG) is a 19-nortestosterone derivative progestin that is highly selective for progesterone receptors and is known for having strong endometrial effects. Visanne (2 mg DNG) leads to a reduction of endometriosis-associated pain and was approved for the treatment of endometriosis in 2010.

The VIPOS study is a post-marketing authorization measure initiated following European approval and uses a similar methodology to the European/International Active Surveillance studies, which previously established the standard for evaluation of post-marketing authorization safety studies for hormonal drug treatments [1]. The study aimed to investigate the safety of DNG for the treatment of endometriosis with a special focus on medical interventions for anemia and the worsening of depressive symptoms associated with the disease.

7. Research question and objectives

The primary objective of the study was to assess safety aspects of DNG2 mg/day (Visanne®) used as endometriosis therapy and of other hormonal treatments for endometriosis in a study population that was representative of 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 were:

- Medical intervention for anemia induced by cyclical bleeding disturbances (anemia)[4]
- First time occurrence of clinically relevant depression, or worsening of existing depression
- To analyze discontinuation patterns of DNG and other endometriosis treatments due to treatment failure (for example re-occurrence of pain, adverse drug reaction)

Secondary objectives are:

- To characterize the baseline risk of users of the individual formulations (lifetime history of co-morbidity, risk markers, co-medication, socio-demographic and lifestyle data).

[4] Anemia associated with endometriosis-related bleeding. For the purposes of this report, this will be referred to as "anemia" for the remainder of the document.

- To analyze the drug utilization pattern of DNG and other 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 of established endometriosis treatments in adolescent women.

8. Amendments and updates

The amendment and updates to the study protocol are specified below. The revised version of the study protocol (dated 21 November 2011) and the protocol amendment (dated 30 September 2017) are included in Annex 1.

Number	Date	Section of the study protocol	Amendment or update	Reason
1	28 FEB 2011	Introduction (1) and Data Analyses (11)	Update (1st revision) Clarification regarding the use of progestins licensed for endometriosis treatment in the European Union (EU). Specification how to assess add-back therapy	Request of the Medicines Evaluation Board (MEB) (Dutch Health Authority)
2	21 NOV 2011	Appendix 1	Update (2nd revision) Modification of the definition of anemia and depression	Request of the Safety Monitoring and Advisory Board
3	30 SEP 2017	Introduction (1), Study Centers (4), Follow-Up (7), Validation of Self-Reported Events (8), Size of the Study and Evaluation (12)	Protocol amendment (Changing of timelines and dates)	Extension of the follow-up phase for one additional year to reach the required observation time

9. Research methods

Briefly, a large cohort of women starting a new hormonal endometriosis treatment (starters, switchers or restarters; cf. Section 9.3), consisting of either DNG 2mg/day or any other hormonal endometriosis treatment, was actively monitored for the occurrence of rare or unexpected adverse outcomes related to the relevant endometriosis treatment.

The primary focus of the active study monitoring was to assess the occurrence of new clinically relevant anemia or depression (including worsening of an existing depression). For the duration of the VIPOS study, patients were monitored continuously for all outcomes of interest (cf. Section 7). All serious adverse events[5] were fully documented and reviewed.

The study was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology (2008), the Good Epidemiological Practice – Proper Conduct in Epidemiologic Research statement issued by the International Epidemiological Association European Federation (2007), the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct for Scientific Independence and Transparency (2010) and the ethical principles based on the Declaration of Helsinki.

Prior to study start, ethical approval was obtained in countries in which it was required (that is, Germany, Hungary, and Switzerland). Non-interventional surveillance studies are not subject to ethical approval in Poland, Russia, and Ukraine.

The study was prospectively registered in the European Union electronic Register of Post-Authorization Studies (EU PAS Registry) of the European Medicines Agency (EMA) on October 21, 2010, under the registration number EUPAS1613 and received an ENCePP Seal. Additionally, the study was registered in the public clinical trials registry of the US National Library of Medicine on December 24, 2010, under the registration number NCT01266421.

9.1 Study design

VIPOS is a large, prospective, non-interventional, long-term cohort study which follows three main cohorts: users of Visanne (DNG), users of other medications approved for the treatment of endometriosis (OAED) in all participating countries - Gonadotropin-releasing Hormone agonists (GnRH-a) and danazol and users of hormonal medications not approved but frequently prescribed for endometriosis treatment (NAED), mainly combined hormonal contraceptives and other progestins. All cohorts consisted of women starting a new hormonal endometriosis treatment (EMT) either as first-ever users (starters) or re-starting EMT after a break of at least 4 weeks (restarter) or switching from another EMT without a break (switcher).

Women were recruited via gynecologists without interfering with the prescribing behavior of the recruiting physicians or with the individual needs of the participating women. This “non-

[5] 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.

interference" approach was used to provide standardized, comprehensive, reliable information on endometriosis treatment patterns.

Physicians who enrolled study participants provided details of the newly prescribed endometriosis treatment, the diagnostic classification and the user status of their patients. All study participants completed a questionnaire at baseline and were then actively contacted every six months for the first year and then annually from year two until the end of the study. Depending on the time of recruitment, patients were followed up between 36 months and 84 months[6]. By means of these contacts, almost all relevant clinical outcomes could be captured. All patient-reported outcomes of interest were validated by contacting the treating physicians and by reviewing relevant source documents by the study team. All reported anemia and depression cases were classified as "confirmed" or "not confirmed" according to a predefined "algorithm (cf. Section 9.12). At the end of this study, this classification was verified by blinded independent adjudication.

9.2 Setting

The VIPOS study was conducted in six European countries: Germany, Poland, Hungary, Russia, Switzerland, and Ukraine.

Recruitment of the cohort members was conducted via a network of more than 1,000 gynecologists managing women with a diagnosis of endometriosis and working either in private practice, specialized endometriosis centers or hospital wards.

Patient recruitment started in December 2010 in Germany and Poland followed by Hungary in early 2011. Because recruitment was slower than projected, additional countries were included to broaden the recruitment base. Recruitment began in Russia and Ukraine at the end of 2011 and in Switzerland in spring 2012. The recruitment target of 25,000 women was achieved at the end of June 2014 (six months later than originally planned), resulting in an extension of the follow-up phase to June 2017.

This recruitment phase of the VIPOS study had yielded a clear picture of the current pharmacological treatment patterns for endometriosis. As expected, a substantial proportion of patients were being treated with combined oral contraceptives. However, the share of patients in the main comparison group of other approved endometriosis drugs was 3.4% instead of the anticipated 10% of the entire study population (5% each for patients treated with either danazol or GnRH-agonists).

The reason for the deficit of patients in the OAED cohort was that danazol was no longer widely prescribed for endometriosis (mainly due to its androgenic side effects). It was removed from many markets but continued to be prescribed in some European countries (including Poland, Russia, and Ukraine). In addition, the prescriptions for GnRH-agonists continued to decline over time.

The expected proportionality of treatments with Visanne, GnRH-agonists, and danazol had formed the basis of the statistical considerations; the low number of patients in the OAED comparator cohorts would impact the power of the study. Therefore, the recruitment emphasis was shifted to

[6] The additional OAED patients who were recruited subsequent to the main recruitment period were followed only for one to two years.

centers with a higher proportion of Visanne, GnRH-a and danazol prescriptions to increase the numbers of patients with these treatments. However, this did not result in the desired increase in the OAED proportion.

ZEG discussed this problem with the members of the Safety Monitoring and Advisory Council in November 2014. The SMAC advised that the recruitment of patients treated with GnRH agonists or danazol should recommence. Accordingly, the recruitment of additional OAED patients began in early spring 2015. The target of 2,000 newly recruited OAED patients was reached in late spring 2016 and this additional, SMAC-advised, recruitment of OAED patients was therefore stopped in June 2016.

However, the slower than expected recruitment of study participants for the VIPOS study during the first two years adversely affected the amount of observation time accumulated through mid-2016. Based on the accrual rates observed until that point in time, it was assumed that the quantitative basis for the analyses as defined by the Study Protocol (that is 84,000 WYs) was not likely to be achieved by the scheduled end of the follow-up phase in mid-2017. It was envisaged that the necessary observation time could be accumulated by prolonging the follow-up phase for an additional year. Therefore, ZEG proposed in the 11th Interim Report and the 12th Interim Report that the follow-up phases should be extended until mid-2018. The SMAC agreed to this prolongation. Accordingly, the last regular follow-ups were initiated at the end of June 2018.

Significant efforts were made to ensure standardized, comprehensive and reliable documentation of baseline (for example patient characteristics and risk factors) and follow-up data (for example treatment use and adverse events).

9.3 Subjects

9.3.1 Protection of Human Subjects

The VIPOS study was conducted in a manner that was consistent with all relevant guidelines and regulations for conducting studies with human subjects, specifically, the latest version of the Helsinki Declaration and the relevant guidelines for “Good Practices”. Steps were taken to protect the privacy of patients and all relevant rules on data privacy were followed.

In countries where required by law or regulation (that is, Germany, Hungary, and Switzerland), the Study Protocol and all study documents were reviewed by ethics committees and approval was obtained prior to the start of recruitment.

The recruiting physicians described to potential study participants the purpose of the study, the non-interventional nature of the study, as well as the length and purpose of the follow-up phase. After having been given an opportunity to discuss the study with the physician and after having been provided with a patient information sheet, patients who agreed to participate signed an informed consent form. The informed consent included permission for the study team to contact the woman’s primary care physician and/or attending physician(s) to obtain medical confirmation (for example, medical reports) of patient-reported serious clinical outcomes. Patients retained the right to withdraw their consent at any time during the study and without the need for explanation.

Study participants were women who were prescribed a new hormonal treatment for endometriosis. The endometriosis diagnosis could either be based on clinical symptoms or on laparoscopic or other surgical findings. Participating physicians discussed the study with the subjects only after the EMT had been chosen. This ensured that participation in the VIPOS study was not considered a requirement for treatment. Women who were eligible for recruitment were asked to participate.

Participating women could be starters (first-ever users of EMT), switchers (users who switched from one EMT to another – without an intake break or an intake break of fewer than 4 weeks), or restarters (users who restarted an EMT after an intake break of at least four weeks). More specific inclusion or exclusion criteria were not made because of the non-interference approach of the study design. All study participants had to complete the self-administered questionnaire in the language of the given country and should be willing to sign an informed consent form and participate in a long-term follow-up study. At the participating centers, women seeking a prescription for a new EMT were asked by their physicians whether they were willing to participate. The physicians explained the nature of the study, its purpose and what participation entailed (including follow-up procedures and the necessity of validating adverse events) prior to study entry. Each woman had ample opportunity to ask questions and was 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 was also provided on a patient information sheet, a data privacy form and an informed consent form which was signed by all study participants.

During the follow-up phase, patients were asked whether they had switched or discontinued EMT use. Information on the date and reason for switching/discontinuation was collected. In this non-interventional study, patients could switch or discontinue use of the prescribed EMT at any time. If they did so, they were nevertheless followed up unless consent was withdrawn. Continuing to follow-up patients who stopped or switched their baseline prescription led to the creation of (sub-) cohorts (for example users of other progestins or ‘no use’) during the follow-up phase.

9.4 Description of analysis sets and user cohorts

As described above, the VIPOS study followed three main cohorts: users of Visanne (DNG), users of other medications approved for the treatment of endometriosis (OAED) and users of non-approved hormonal medications prescribed for endometriosis treatment or those approved only in some participating countries (NAED).

The OAED cohort consisted of GNRH agonists and danazol users (which formed (sub-)cohorts in the analysis). The majority of study participants had been prescribed a non-approved hormonal medication for endometriosis treatment. After analyzing this large user cohort comprised of several groups of medications (cf. Section 10.2), the SMAC advised forming (sub-)cohorts of combined hormonal contraceptives (CHC), other progestins (progestins other than DNG) and other NAED (comprising the remaining medications). The latter (sub-)cohort is small and is not shown separately in the descriptive analysis (but it is included within the “all NAED” user cohort).

A small group of study participants was included with more than one hormonal medication for endometriosis treatment (concomitant medication). These users were assigned to the “allocation unknown” group. This group does not include GnRH-a users who received an add-back therapy from the start.

The cohorts consist of women who started a hormonal medication for endometriosis for the first time in their lives (starters), women who switched from one EMT to another without an intake break of at least four weeks (switchers) and women who restarted endometriosis treatment after a break of at least four weeks (either with the previous EMT or with another one) (restarters).

The EMT user status was considered in the analysis. Baseline characteristics, as well as follow-up results, were shown for (1) the complete cohort (all users), (2) starters, (3) switchers and (4) restarters (cf. Annex 1.6, Volume of tables).

Due to the differences in patient characteristics between the participating countries, both SMAC and the Medicines Evaluation Board (MEB) requested a stratification of results by country.

SMAC recommended in June 2014 that further subsets be defined based upon the classification of endometriosis. Specifically, surgically confirmed cases were to be assessed separately from cases with a clinical diagnosis which was made by the treating physician (and which was, therefore, not standardized across sites).[7]

After study entry, each woman could switch or stop EMT use (temporarily or permanently) as they wished (for example due to a planned pregnancy or side effects). All study participants (including pregnant women) remained in the follow-up phase until the end of the study (unless they withdrew their informed consent). Therefore, in addition to the three main cohorts and their respective (sub-)cohorts, a cohort of "Ex-use" was included in the analysis of follow-up data.

As previously described (cf. Section 9.10.2), safety conclusions in this report are based on an as-treated (AT) analysis. Women who were exposed to multiple endometriosis medications ("multi-users") or unspecified treatments were categorized as "allocation unknown". Women who stopped their treatment for at least three months were assigned to the "Ex-use" cohort.

[7] The stratified results by classification of diagnosis are included in Annex 1.6, Volume of Tables.

9.5 Variables

The variables for analyses were derived from the baseline and follow-up questionnaires (included in Annex 1) as listed below.

Item/Variable	Baseline		Follow-up
	Physician	Patient	Patient
Patient characteristics			
Identification number		x	x
Date of birth (→ Age)		x	
Height		x	
Weight (→ BMI)		x	x
Date of completion of the questionnaire		x	x
Socio-economic characteristics			
Educational level		x	
Smoking status (number of cigarettes/day)		x	
Endometriosis characteristics and treatment			
Classification of diagnosis	x		
Endometriosis medication prescribed at study entry	x		
User status	x		
No. of surgical procedures related to endometriosis in the last 2 years	x		
Endometriosis symptoms (type, first occurrence)		x	
Date of endometriosis diagnosis		x	
Severity and impact of endometriosis-related pain		x	
Previous endometriosis treatment (surgical procedures, medication, other measures)		x	
Hormonal endometriosis medication used after study entry			x
Reason for stopping/switching endometriosis medication (trying to become pregnant, treatment duration finished, medication ineffective, side effects-which, other reasons – which)			x
Gynecological history			
Age at menarche		x	
Number of pregnancies/live births/ abortions/still births		x	
Delivery during follow-up, problems with the newborn			x
Medical history/current health status			
Severe diseases/conditions		x	x

Item/Variable	Baseline		Follow-up
	Physician	Patient	Patient
Surgical procedures (other than endometriosis-related)		x	x
Anemia		x	x
Depression		x	x
Hospital admission (planned/unplanned, reason)			x
Mood			
Feeling down, like a failure, optimistic in the last 4 weeks		x	x
Family history			
Endometriosis, depression, VTE		x	
Regular use of concomitant medication		x	x

9.5.1 Exposure

The VIPOS study followed women initiating a new hormonal treatment for endometriosis (EMT). Data collection on exposure included the EMT prescribed at study entry as well as subsequent use of EMT(s) during follow-up. Study participants were requested to record the brand name(s) and the duration of use (from MMYYYY – to MMYYYY) of the EMT(s) used during the relevant follow-up period. If they stopped or switched, they were asked for the reason(s) of treatment discontinuation. Based on these data, a "calendar" for each study participant was created covering each month of study participation with the respective code for the EMT used (including a code for "no use"). The code list for EMT included the allocation to the main cohorts of interest (DNG, OAED, NAED) and the (sub-)cohorts (GnRH-a, Danazol, CHC, other progestins, other NAED). Additionally, details such as the method of application and the active agent were recorded.

9.5.2 Outcome

Study outcomes included depression (new depression and worsening of an existing depression), anemia and other significant and serious adverse events which occurred during the study period. Outcomes of interest were validated and categorized as "confirmed" or "not confirmed" (cf. Section 9.12). The results of the validation process were captured in the event validation database.

In addition to EMT use (cf. Section 9.5), reasons for treatment discontinuation (for example side effects) were captured during follow-up and coded to facilitate their categorization and summation.

Treatment failure as one of the primary outcomes was defined as discontinuation of treatment due to side effects or a perception that the medication was ineffective.

9.5.3 Covariates

To assess the potential for confounding the following covariates were taken into consideration in the analysis of anemia: age, history of bleeding disorders (reported amongst the endometriosis-related symptoms) and personal history of anemia.

Covariates for the analysis of depression included age, personal and family history of depression and prior use of an antidepressant.

In the analysis of treatment discontinuation due to treatment failure covariates included age, family and personal history of depression and severity of endometriosis-related pain.

9.6 Data sources and measurement

Baseline data relating to study participants' state of health and potential risk factors were recorded on a self-administered questionnaire at study entry. Participants were asked to provide their medical history (with a special focus on endometriosis).

Physicians provided information on the prescribed endometriosis treatment at study entry, the type of endometriosis diagnosis (based on symptoms or surgically confirmed), user status (first-ever user, re-starter or switcher) and the number of endometriosis-related surgical procedures within the last two years before study entry.

In addition to the baseline variables described in Section 9.5, study participants provided their addresses, phone numbers, and email addresses. They were also requested to provide the contact details of a friend or relative who could be contacted if it was not possible to reach the study participant[8]. In compliance with data privacy regulations, these data were documented on a separate sheet. These sheets and the electronic representations of their content were stored separately from the baseline questionnaires and their respective electronic representations. These data privacy requirements applied to all relevant study procedures, including the archiving of documents and databases at the end of the study.

Follow-up assessments for each woman in the VIPOS study were scheduled to be conducted every six months for the first year and annually thereafter. Questionnaires were either mailed to the women or the questions were asked via telephone interview (via **C**omputer **A**ssisted **T**elephone **I**nterview - CATI). The latter method was utilized in Russia and Ukraine. The study participants in Hungary and Russia were also offered the option of completing the follow-up questionnaire online (CAWI). The Russian study participants were also given the opportunity to answer the follow-up questions on their mobile phones (MAWI).

The follow-up questionnaires addressed the occurrence of adverse events, and in particular, events meeting the criteria for seriousness, reasons for discontinuing EMT use or switching to another hormonal endometriosis medication. The variables recorded at each follow-up are described in Section 9.5.

The questionnaires were collected in each country by local study teams and reviewed for completeness and plausibility/consistency of the responses. Manual checks were made on paper questionnaires and specific checks were implemented on questionnaires captured electronically. Missing and inconsistent information was clarified directly with the women via telephone if possible.

[8] This information was not mandatory and not all women provided it.

First data entry of the data captured via paper questionnaires was done by the local study teams. Data from questionnaires completed via CATI or online were transferred to the study database provided by ZEG. These procedures were validated beforehand as described in Section 9.11. The completed questionnaires and the local databases which contained the questionnaire response data and the study status of the women were then forwarded to ZEG in Berlin. At ZEG all incoming data were subjected to comprehensive quality control checks. Unclear or inconsistent information was described in detailed queries which were forwarded to the local study teams for clarification with the women. ZEG monitored and endorsed the timely processing of the queries. As an additional quality control, an independent second data entry was performed at ZEG. As part of the data verification process, all inconsistent data entries were corrected, and all changes documented. A data review was conducted by the Principal Investigator before final analysis.

9.7 Bias

Potential types of biases inherent in the study design are discussed in detail in Section 11.2 “Limitations”.

9.8 Study size

The study was designed to analyze rare events (according to the CIOMS classification one to 10 events per 10,000 women-years). However, the specific adverse events considered in relation to the sample size calculations were anemia, clinically relevant depression and treatment failure.

Based on a 10-15% background prevalence of anemia in premenopausal European women [2] and the fluctuating nature of this disease, the sample size calculation was based on an incidence of 0.01 (equivalent to 100 events per 10,000 WY).

The expected incidence rate for newly diagnosed or worsening depression was at least 0.01 (100 events in 10,000 WY) based on an estimated prevalence rate of 20% for depression in women with endometriosis [3-5].

It was anticipated that the majority of women would stop or change treatment regimens during the course of this study. Subsequently, for women stopping or changing endometriosis treatment (‘treatment failure’) due to lack or loss of efficacy or an adverse drug reaction (“side effects”), an incidence rate of at least 0.3 (equivalent to 3,000 events per 10,000 WY) was expected.
For the DNG cohort, a proportion of 0.25 of the total study population seemed to be realistic.

Overall, three hypotheses were to be tested. The problem of multiple comparisons was addressed by using Bonferroni-Holm correction to maintain the overall error rate by testing each individual hypothesis at a statistical significance level of 1/3 times what it would be if only one hypothesis were tested (that is, the individual tests will be based on an α level of 0.0167 instead of 0.05).

The follow-up of 25,000 women for three to six years was expected to result in about 89,000 women-years. This estimate was based on the following assumptions: (1) ZEG’s physician network could recruit 25,000 women within three years with an annual recruitment rate of more

than 8,300 women and (2) an annual drop-out rate of 10% according to the results of the EURAS-OC and LASS studies.

Power calculations based on the expected incidences for anemia and depression showed that approximately 84,000 women-years would be sufficient to show non-inferiority of DNG versus other endometriosis medications for anemia and depression. Accordingly, the study was powered to exclude a two-fold risk of anemia and clinically relevant depression for DNG assuming that DNG accounts for at least 10% of the total exposure and the true risk of anemia and depression are not different between the DNG and the OAED cohorts.

Table 1: Power calculations for anemia and depression based on the assumption that the true incidence of DNG cohort is no different from other endometriosis medications (reference cohort)

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

It was calculated that approximately 29,500 WY would be required to show that DNG is superior to other endometriosis medications with regard to ‘treatment failure’ assuming that the proportion of DNG, danazol, and GnRH agonists users each account for 10% of the total exposure.

Table 2: Power calculation 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 the other endometriosis medications cohort.

Test significance level, α (one-sided)	0.0167
Incidence of treatment failure for other endometriosis medications 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 the study population)	10
Proportion of reference users (% of the study population)	5
Required women-years in DNG cohort	2,950
Required women-years in other endometriosis medications cohort	1,475
Total women-years	29,500

9.9 Data transformation

Two different databases were used for data collection to ensure compliance with data privacy regulations: the administrative database (ADB) and the study database (SDB).

The administrative database contained the personal data (for example names and addresses) of the recruiting physicians and the study participants and was maintained by ZEG's field organization in each participating country. The ADB was not transferred to ZEG in Germany but remained in the countries. The SDB did not contain any subject personal identifying information; it contained all baseline questionnaire and follow-up questionnaire data.

Event data were derived from the questionnaire data entered into the study database. All disease diagnoses were coded using the ICD10 (International Classification of Diseases)[9]. Additional codes were used for data/events of specific interest (for example, categories for confirmed and not confirmed depression and anemias). Concomitant medication was coded using WHO ATC codes. Surgical procedures were coded using the modified operation and procedure coding list (OPS) provided by DIMDI (German Institute for Medical Documentation and Information).

Exposure data were used to identify for each study participant the relevant cohorts and (sub-) cohorts for each exposure period (period of continuous use of one specific hormonal endometriosis treatment - cf. Section 9.5.2).

[9] International statistics on morbidity and mortality are normally based on ICD10 coding; this coding was therefore used in this study to facilitate comparisons of incidence rates in several countries. Furthermore, hospital discharge diagnoses and causes of death on death certificates were frequently provided in ICD10.

Simple data transformations were also necessary for the calculation of BMI from the variable's height and weight and for the calculation of age from study entry date and the date of birth.

9.10 Statistical methods

9.10.1 Main summary measures

Main summary measures are described in Section 9.10.2.

9.10.2 Main statistical methods

Statistical analyses were conducted based on the "as treated" (AT) population as well as the "intention to treat" (ITT) population. For the AT analyses, data on outcomes of interest were assigned to the medication used by the respective study participant at the time of the event. For the ITT analyses, all data from individual participants were assigned to the medication prescribed at study entry, regardless of any switching (or stopping) or of any different (or no) medication being used at the time of the event.

For studies on efficacy, the ITT approach is often preferred because it is conservative with respect to the superiority of a new treatment. For a drug safety study, however, the ITT approach dilutes differences between treatments. Therefore, the investigators and the Safety Monitoring and Advisory Council designated the AT analysis as the primary analysis for the assessment of the VIPOS study data.

Baseline population characteristics were described by absolute and relative numbers per user cohort and basic summary statistics (mean, standard deviation, minimum, maximum, 25th percentile, 50th percentile (median), and 75th percentiles). In addition, age-standardized proportions were calculated for age-dependent variables.

For the analysis of follow-up data, woman-years of exposure were calculated based on treatment information received from the study participants. Incidence rates are shown for all outcomes of interest including recurrent events. Incidence rate ratios between (sub-)cohorts are presented for the primary outcomes of anemia and depression. The incidence of treatment failure is shown as the incidence proportion per 100 treatment starts. Exact 95%-confidence intervals were calculated according to Clopper & Pearson (1934) [6].

Inferential statistics for anemia and depression were based on Cox proportional hazards models. Crude hazard ratios between cohorts were calculated for these outcomes of interest. If the numbers allowed for stable estimates, adjustment for potential confounding was performed by including predefined prognostic factors as covariates in the Cox proportional hazard models. For each of the outcomes of interest, a limited number of prognostic factors were chosen by the members of the Safety Monitoring and Advisory Council based on their expertise (denoted as 'expert' model). The outcome-specific co-factors are described in the relevant sub-sections of Section 10.3 ('Main results'). For example, for clinically relevant depression the Council chose age, personal and family history of depression and previous use of antidepressants. Assessment of the results and conclusions were primarily based on the 'expert' models. Country has been considered as a random source of variance and was included as a stratum.

The analysis of treatment failure was not based on time-to-event because of variation in the recommended duration of use for different medications. Treatment failure may occur at multiple points in time during follow-up if multiple successive treatment episodes are present. Clustering per subject is accounted for within the application of generalized estimating equations (GEE) [7]. Crude and adjusted odds ratios were calculated.

All statistical analyses were performed using SAS 9.4.

9.10.3 Missing values

Investigators in real-world studies are frequently confronted with a situation of missing data. There are many reasons why study participants might not provide data, some of which include a superficial reading of the questions, misunderstanding of the questionnaire or simply unwillingness to give certain information.

The VIPOS study used questionnaires with a clear layout to guide the study participants and which were designed to encourage them to answer even intimate questions. Most questions had been tested in several previous studies with large populations. In order to reduce the amount of missing information, participants were contacted several times. If the missing information could also be collected by the enrolling physicians (for example information on prescription, details of diagnosis, etc.), they were contacted. If these strategies were unsuccessful, missing data were presented in the respective table categories and were not imputed or carried forward in any statistical analysis. An exception to this rule was missing values related to the three ´Mood questions´[10] where on the specific request of the Safety Monitoring and Advisory Committee, a last observation carried forward (LOCF) approach for analysis was used.

Women with concomitant use of medications or unspecific treatment were specified as “Allocation unknown”.

9.10.4 Sensitivity analyses

To assess the robustness of the statistical models, several sensitivity analyses were performed. Regarding inferential statistics, the Safety Monitoring and Advisory Council had previously defined the prognostic factors for inclusion in generalized regression models. To investigate the impact of the predefined prognostic factors, a backward stepwise approach was used where all potential confounders were included.

Sensitivity analyses for the depression outcome were requested by SMAC as follows:

- Stratification by age: <25 years/ ≥25 years
- Analysis considering only confirmed cases with no history of depression at all and no previous use of antidepressants.
- Analysis combining confirmed and potential cases of depression.

[10] See SAP Section 5.5

- Analysis combining confirmed cases and cases treated by a general practitioner with antidepressants (not confirmed according to the study definition).

Sensitivity analyses for the treatment failure outcome were requested by SMAC[11] as follows:

- Analysis of treatment discontinuation separately for (1) "medication ineffective" (mainly seen as treatment failure) and (2) "side effects".
- Analysis of *treatment failure* within the first 6 months of a treatment episode to compare with the OAED cohort. GnRH-a is predominantly used for 6 months and Danazol is not advised for continuous long-term use.

9.10.5 Amendments to the statistical analysis plan

The statistical analysis plan (SAP) was reviewed by the Safety Monitoring and Advisory Council in December 2012.

Since then changes were made in accordance with requests from the Medicines Evaluation Board and the SMAC (that is, stratification by country, stratification by classification of endometriosis diagnosis, further sub-classification of cohorts as well as a description of Visanne long-term users). The revised SAP was approved by SMAC members at the beginning of November 2018.
The final version of the SAP is part of Annex 1.

9.11 Quality control

ZEG Berlin has established numerous quality assurance procedures. Internal audits were conducted to ensure that ZEG Berlin complies with Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology (GPP), Good Epidemiological Practice issued by the European Epidemiology Federation (GEP), Good pharmacovigilance practices issued by the EMA (GVP), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct, the Nuremberg Code and the Declaration of Helsinki. ZEG Berlin also conducted site audits of the local field organizations in the respective countries for the VIPOS study. These audits involved organizational aspects, compliance with the working procedures and source data checks (informed consent forms and questionnaires).

ZEG Berlin's internal Standard Operating Procedures (SOPs) Manual describes standardized working procedures to ensure the quality of a high standard and compliance with all applicable guidelines. The SOPs are reviewed every four years and updated as necessary to ensure that all

[11] No sensitivity analyses were requested for anemia.

processes are in line with legal compliance and data integrity. Each employee is expected to apply the SOPs with an understanding of the underlying principles.

All processes relevant for legal compliance of the study or the integrity of the data were subject to quality control measures during the VIPOS study. These included (1) development of a study protocol, questionnaires, databases and data entry screens, (2) data entry, (3) plausibility checks, (4) validation of clinical outcomes, (5) adverse outcome reporting, (6) data analysis, (7) report writing, (8) publication of results, (9) archiving of study materials (that is all baseline/follow-up questionnaires, other study documents, and electronic files). All quality control measures were based on the four-eye principle.

For follow-up data, some field organizations combined the paper-based approach with electronic data capture methods (EDC) such as online follow-up questionnaires (for example CAWI for computers and MAWI for smart phones) or paperless computer-assisted telephone interviews (CATI). Before implementation, the electronic follow-up questionnaire, data collection, processing and export/import were tested by ZEG using functional testing. After successful testing, ZEG Berlin approved the approaches which were then used in the field.

ZEG Berlin used an external auditor who is responsible for systematically reviewing the quality standards implemented at ZEG Berlin and the local field organizations in the participating countries. The external auditor also proposed suitable improvements to quality standards. During study conduct, the external auditor examined the consistency between ZEG Berlin's electronic database and the original questionnaires as part of the site audits. In Russia and Ukraine, CATI was used and the interviews were recorded. As part of the audits, a sample of voice records was checked for consistency with the data in the ZEG database. None of these checks conducted during site audits resulted in serious findings.

ZEG Berlin’s conduct of the VIPOS study was overseen throughout the duration of the study period by a Safety Monitoring and Advisory Council (SMAC) comprised by internationally acknowledged experts in the fields of gynecology & obstetrics, psychiatry, and epidemiology (cf. Section 4). The committee made recommendations and final decisions relating to all scientific matters.

9.12 Validation of self-reported events

A self-administered participant questionnaire completed at frequent intervals is a very sensitive tool that captures almost all serious clinical outcomes. From a methodological point of view, it captures a much higher proportion of these outcomes than methods relying only on the prescribing gynecologists who often are not involved in the diagnosis and treatment of these outcomes. However, self-administered reports have poor specificity: there is a large difference between the rates of reported versus validated events, because laypersons often misclassify adverse events (such as 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). Consequently, this type of inaccuracy in patient reports requires careful validation.

If an SAE or any other outcome of interest was reported by a study participant, the follow-up questionnaire also captured the subjectively perceived symptoms, the signs of disease, and wherever possible the diagnosis as understood by the patient. The woman was also requested to provide the name and address of the attending physician or hospital where she was treated.

Follow-up questionnaires containing information on relevant events were passed to the medical reviewer group. If information was unclear or missing, the woman was contacted (via telephone, email, etc.). For many events, it was necessary to contact the diagnosing and/or treating physician for clarification and validation of the patient-reported information. This procedure was mandatory for all potential serious adverse drug reactions, including depression and anemia.

Under routine medical conditions, diagnosis of an SAE is not always confirmed by a diagnostic method with high specificity. Therefore, SAEs were classified by the investigators as "confirmed" (definite and probable event) or "not confirmed" according to the following predefined algorithm:

- Definite Event:

  Confirmed by diagnostic measures with high specificity (for example, phlebography for DVT, spiral CT for pulmonary embolism, cerebral MRT for cerebrovascular accidents, histology in case of cancer).

- 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.

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

For classification of medically treated anemia and clinically relevant depression the definition of "definite", "probable" and "not confirmed" was further specified as follows:

Anemia

- Definite Event:
  - Confirmed by repeated reliable laboratory test (for example hemoglobin, packed cell volume), plus pertinent therapy (blood or iron transfusion, iron tablets) and
  - No obvious explanation (such as gastrointestinal bleeding, trauma, major surgery) or no explanation other than endometriosis-related bleeding

- Probable Event:
  - No reliable laboratory data available, but clinical diagnosis stated by a physician, followed by pertinent therapy (see above) and
  - No obvious explanation (such as gastrointestinal bleeding, trauma, major surgery) or no explanation other than endometriosis-related 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

Clinically relevant Depression

- Definite Event:
    - Diagnosis is confirmed by a physician specialized in psychiatry using validated instruments (for example HAM-D, BECK depression inventory) whereby bipolar disorders and schizoaffective disorders were excluded
    - Confirmed suicide or attempted suicide in a participant with a prior history of depression

- Probable Event:
    - Clinical diagnosis confirmed by a physician specialized in psychiatry without the use of validated instruments whereby bipolar disorders and schizoaffective disorders were excluded
    - Confirmed (attempted) suicide without a previous psychiatric diagnosis

Definite and probable events were classified as “confirmed events”.

- 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 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

For the purpose of continuously monitoring safety data during the study, the investigators classified all reported cases of anemia and depression. For the final analysis this classification was verified by an independent blinded adjudication process (cf. Section. 9.13)

9.13 Blinded Adjudication of anemia and depression

In order to minimize classification bias – particularly if selectively affecting individual exposure cohorts – the classification of self-reported anemia and depression into confirmed and not

confirmed cases was adjudicated by two blinded medical boards prior to the final analysis. The 'Hematology Board' consisted of three independent medical experts specialized in internal medicine/hematology and gynecology. The 'Depressive Illness Board' consisted of specialists in psychiatry/psychological medicine. They reviewed all available information on the reported cases of anemia and depression, respectively. Brand names, dose, regimen, and composition of the endometriosis medication used by the reporting woman was rendered anonymous. The adjudicators performed the review independently of each other and without knowing the judgment of the other adjudicators. If at least one adjudicator classified a report as a confirmed case of anemia or depression, the reported event was considered 'confirmed'.

10. Results

10.1 Descriptive data

A total of 31,506 women were recruited by 1,012 active centers (that is, gynecologists or specialized centers who recruited at least one patient) for the VIPOS study. Overall, 3,666 of these women (11.6%) were excluded due to protocol violations (for example, incomplete informed consent form) or because they had already been enrolled in the study by the same or different study centers (that is, duplicate enrollments of the same women). The remaining 27,840 quality-controlled computerized data sets from the women (one per woman) with baseline information were analyzed and form the intention-to-treat (ITT) population. However, 1,410 study participants reported during the follow-up that they did not start their baseline prescription, mainly due to concerns about side effects. These 1,410 datasets are excluded from the "as-treated" (AT) population. Table 3 shows that there are no substantial differences between the ITT and AT population regarding the distribution of the cohorts.

At study entry, 3,251 women (11.7%) received a prescription for DNG, 3,467 women (12.5%) a prescription for either GnRH-a or danazol (OAED) and 21,100 women (75.8%) were enrolled with a hormonal medication not approved for endometriosis treatment (NAED). A total of 22 women were prescribed an endometriosis treatment consisting of more than one hormonal concomitant medication (0.1%).

A total of 94,602 validated follow-up questionnaires (comprising a total of 86,227 women-years of observation) were included in the final analysis.

Table 3: ITT and AT population by cohorts and (sub-)cohorts

Cohort	ITT		AT	
	N	%	N	%
DNG	3,251	11.7	3,023	11.4
All OAED	3,467	12.5	3,371	12.7
GnRH-a	2,578	9.3	2,542	9.6
Danazol	889	3.2	829	3.1
All NAED	21,100	75.8	20,016	75.8
CHC	17,516	62.9	16,638	63.0
Progestins	3,437	12.4	3,246	12.3
Other NAED	147	0.5	132	0.5
Allocation unknown	22	0.1	20	0.1
Total	27,840	100.0	26,430	100.0

*Discrepancy due to rounding.

The ITT and the AT populations were also similar with regard to the mean age, the user status and the classification of the endometriosis diagnosis as shown in Table 4, Table 5 and Table 6.

Table 4: ITT and AT population by mean age

	DNG	OAED	NAED	Total
Number (%) of women in ITT population	3,251 (100%)	3,467 (100%)	21,100 (100%)	27,840 (100%)
Number (%) of women in AT population	3,023 (100%)	3,371 (100%)	20,016 (100%)	26,430 (100%)
Age in years (ITT population)				
Mean	35.1	37	31.9	32.9
SD	7.78	8.20	9.03	8.98
Age in years (AT population)				
Mean	35.1	37	31.9	32.9
SD	7.70	8.19	9.01	8.96

Table 5: ITT and AT population by classification of diagnosis

	DNG	OAED	NAED	Total
Number (%) of women in ITT population	3,251 (100%)	3,467 (100%)	21,100 (100%)	27,840 (100%)
Number (%) of women in AT population	3,023 (100%)	3,371 (100%)	20,016 (100%)	26,430 (100%)
Diagnosis classification (ITT population)				
Based on clinical symptoms	1,745 (53.7%)	2,601 (75.0%)	20,068 (95.1%)	24,433 (87.8%)
Confirmed by surgery	1,506 (46.3%)	866 (25.0%)	1,032 (4.9%)	3,407 (12.2%)
Diagnosis classification (AT population)				
Based on clinical symptoms	1,608 (53.2%)	2,544 (75.5%)	19,057 (95.2%)	23,227 (87.9%)
Confirmed by surgery	1,415 (46.8%)	827 (24.5%)	959 (4.8%)	3,203 (12.1%)

Table 6: ITT and AT population by user status

	DNG	OAED	NAED	Total
Number (%) of women in ITT population	3,251 (100%)	3,467 (100%)	21,100 (100%)	27,840 (100%)
Number (%) of women in AT population	3,023 (100%)	3,371 (100%)	20,016 (100%)	26,430 (100%)
User status (ITT population)				
Starter	2,374 (73.0%)	3,107 (89.6%)	16,741 (79.3%)	22,240 (79.9%)
Switcher	279 (8.6%)	71 (2.0%)	1,184 (5.6%)	1,534 (5.5%)
Restarter	598 (18.4%)	289 (8.3%)	3,175 (15.0%)	4,066 (14.6%)
User status (AT population)				
Starter	2,197 (72.7%)	3,026 (89.8%)	15,957 (79.7%)	21,196 (80.2%)
Switcher	259 (8.6%)	69 (2.0%)	1,116 (5.6%)	1,444 (5.5%)
Restarter	567 (18.8%)	276 (8.2%)	2,943 (14.7%)	3,790 (14.3%)

ITT and AT population differ with regard to the number of study participants and subsequently to the number of women-years.

Table 7 illustrates the difference in observation time between the AT and ITT population.

Table 7: ITT and AT population by observation time

Cohort	Women-years	
	AT	ITT
DNG	4,482	10,920
GnRH-a	1,694	5,317
Danazol	750	2,040
CHC	33,806	57,845
Other progestins	5,753	9,468
Other NAED	532	569
Ex-use	36,877	
Allocation unknown	293	68
Total	**84,187**	**86,227**

In the ITT approach, the observation time was counted according to the EMT prescribed at study entry. The "Ex-use" was, therefore, not applicable.

In the AT population 59% of the participating women in all three main cohorts combined discontinued their treatment either temporarily or ultimately contributing 36,877 women-years as "ex-users". Thereby, the proportion of "ex-use" in the total number of women-years was substantially higher than expected.

The outcome data were reported according to the treatment at the time of the event ("as treated"). Therefore, the baseline characteristics are described for the AT population only. Based on the final SAP, the Volume of Table (Tables of results) in Annex 1 displays all baseline characteristics for the AT and the ITT population.

The majority of the participants (75.8%) in this non-interventional study were enrolled with a hormonal medication not approved for endometriosis treatment[12] (Figure 1). Combined oral contraceptives (COC) were most commonly prescribed, mainly in an extended regimen. The SMAC suggested grouping all combined contraceptives (including non-oral) into the (sub-)cohort "Combined Hormonal Contraceptives" (CHC). Following the SMAC suggestion, the (sub-)cohort "Other progestins" contains all progestin-only products as follows: progestin medications, progestin-only pills (normally used for contraception) as well as the levonorgestrel-containing IUS Mirena, the medroxyprogesterone acetate injections and etonogestrel-containing implants. The most frequently prescribed progestin medication was Duphaston (dydrogesterone) which is approved for endometriosis treatment in Poland, Russia and Ukraine but not in the other participating countries. The (sub-)cohort "Other NAED" encompasses the remaining medications, which were mainly hormone replacement therapy (HRT) drugs but also included a small number of ulipristal acetate

[12] If a medication was approved for endometriosis treatment in some, but not in all, participating countries it was considered "not approved".

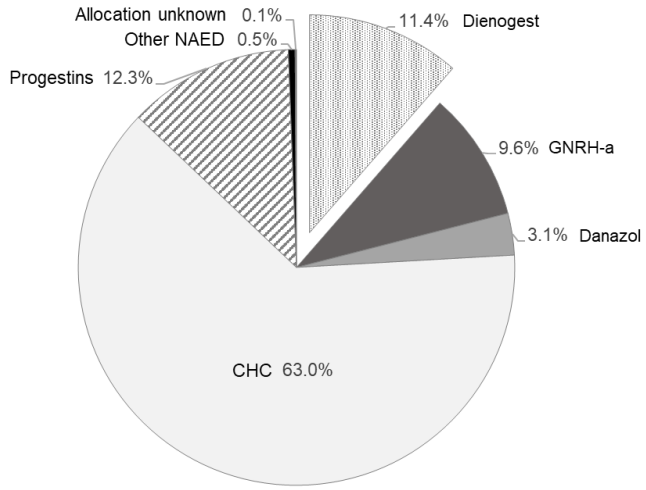
prescriptions. The numbers and percentages of the different types of medications in relation to the entire NAED cohort are displayed in Table 8.

Table 8: Description of the NAED cohort, numbers, and percentages

Class of medication	N	%	Cohort
Combined Oral Contraceptives	15,993	79.90	CHC
thereof COC in extended regimen	11,997	59.94	
Combined vaginal ring	617	3.08	
Combined patch	28	0.14	
Progestins medication	2,063	10.31	Other Progestins
thereof Dydrogesterone	1,559	7.79	
POP	432	2.16	
LNG IUS	592	2.96	
MPA injections	156	0.78	
Implant (ENG)	3	0.01	
Remaining NAED (HRT, ulipristal acetate)	132	0.66	Other NAED
Total	**20,016**	**100.00**	**All NAED**

The cohort of "Other approved endometriosis drugs" OAED was divided into the two (sub-)cohorts of interest: GnRH-a and danazol. A very small group of the study participants (22 women, mainly from Ukraine) received a prescription for two endometriosis medications (for example, DNG 2 mg and dydrogesterone, DNG 2 mg and lynestrenol 5 mg). As advised by the SMAC, study participants with concomitant use of medication are classified as "Allocation unknown". The distribution of the study population by (sub-)cohorts at study entry is shown in Figure 1.

Figure 1: Study population by (sub-)cohorts



The treatment allocation by (sub-)cohorts differed between the participating countries as shown in Table 9.

Table 9: Regional distribution by (sub-)cohorts

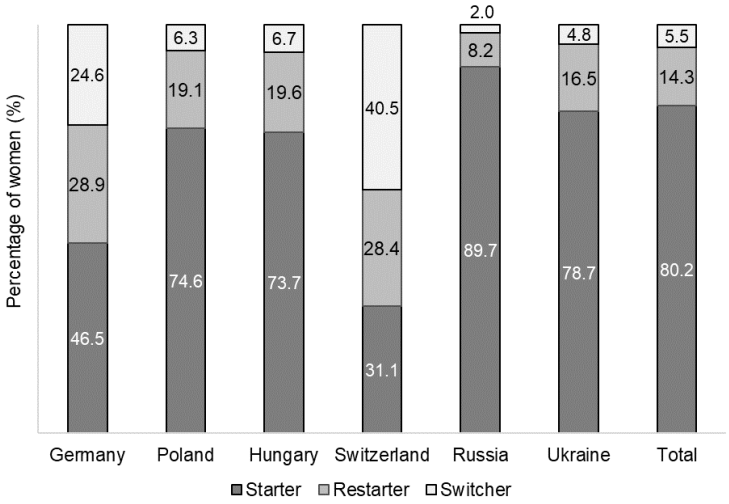
	DNG	OAED			NAED			Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED		
Number (%) of women	3,023 (100%)	2,542 (100%)	829 (100%)	3,371 (100%)	16,638 (100%)	3,246 (100%)	20,016 (100%)	20 (100%)	26,430 (100%)
Germany	454 (15.0%)	75 (3.0%)	0 (0.0%)	75 (2.2%)	871 (5.2%)	313 (9.6%)	1,187 (5.9%)	1 (5.0%)	1,717 (6.5%)
Poland	525 (17.4%)	10 (0.4%)	75 (9.0%)	85 (2.5%)	303 (1.8%)	36 (1.1%)	342 (1.7%)	2 (10.0%)	954 (3.6%)
Russia	1,039 (34.4%)	1,778 (69.9%)	234 (28.2%)	2,012 (59.7%)	7,753 (46.6%)	2,120 (65.3%)	9,957 (49.7%)	0 (0.0%)	13,008 (49.2%)
Hungary	631 (20.9%)	410 (16.1%)	0 (0.0%)	410 (12.2%)	6,980 (42.0%)	241 (7.4%)	7,246 (36.2%)	0 (0.0%)	8,287 (31.4%)
Switzerland	62 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (0.0%)	4 (0.1%)	12 (0.1%)	0 (0.0%)	74 (0.3%)
Ukraine	312 (10.3%)	269 (10.6%)	520 (62.7%)	789 (23.4%)	723 (4.3%)	532 (16.4%)	1,272 (6.4%)	17 (85.0%)	2,390 (9.0%)

The number of women recruited per country was influenced by the study start date within each country, the size of the country's population, and the willingness of the prescribing gynecologists and specialized endometriosis centers to participate in the VIPOS study. Due to an insufficient number of women enrolled in Switzerland (n=74), data relating to this country should be interpreted with caution.

At study enrollment, 80.2% of women received a hormonal medication for the treatment of endometriosis for the first time (starters), 5.5% switched hormonal medication without a treatment break of at least four weeks (switchers) and 14.3% had a treatment break in hormonal endometriosis treatment of at least four weeks before study entry (re-starters). Starters formed the majority of the study population in every country: Germany (46.5%), Poland (74.6%), Hungary (73.7%),

Switzerland (31.1%), Russia (89.7%), and Ukraine (78.7%). Figure 2 shows the user status by country.

Figure 2: User status by country



The cohorts differ substantially in relation to age distribution. The users of OAED have a higher mean age (37.0 years) compared to DNG users and users of NAED (35.1 and 31.9 years, respectively.) The mean age of the complete study population is 32.9 years. For the NAED cohort, the proportion of women under the age of 20 and in the age group 20 to 29 years is much higher than in the other two cohorts as shown in Table 10.

Table 10: Age profile by (sub-)cohorts

	DNG	OAED			NAED			Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED		
Number (%) of women	3,023 (100%)	2,542 (100%)	829 (100%)	3,371 (100%)	16,638 (100%)	3,246 (100%)	20,016 (100%)	20 (100%)	26,430 (100%)
Age (years)									
Mean (SD)	35.1 (7.7)	37.5 (8.43)	35.5 (7.18)	37 (8.19)	30.9 (8.8)	36.9 (7.9)	31.9 (9.01)	37.9 (8.38)	32.9 (8.96)
Median	34.6	36.4	35.5	36.2	30.1	37	31.7	37.7	32.9
Age category									
< 20 years	48 (1.6%)	15 (0.6%)	10 (1.2%)	25 (0.7%)	1660 (10.0%)	57 (1.8%)	1717 (8.6%)	0 (0.0%)	1790 (6.8%)
20 to < 30 years	764 (25.3%)	458 (18.0%)	187 (22.6%)	645 (19.1%)	6623 (39.8%)	576 (17.7%)	7202 (36.0%)	4 (20.0%)	8615 (32.6%)
30 to < 40 years	1399 (46.3%)	1212 (47.7%)	417 (50.3%)	1629 (48.3%)	5368 (32.3%)	1425 (43.9%)	6811 (34.0%)	8 (40.0%)	9847 (37.3%)
>= 40 years	812 (26.9%)	857 (33.7%)	215 (25.9%)	1072 (31.8%)	2987 (18.0%)	1188 (36.6%)	4286 (21.4%)	8 (40.0%)	6178 (23.4%)

There were also differences in mean age between the countries. The study population in Hungary was the youngest with a mean age of 27.5 years, this was approximately three years younger than Switzerland (30.1 years), Germany (31.1 years) and Poland (31.6 years) and 10 years younger than

the study population in Russia (36.0 years) and Ukraine (36.9 years). (cf. Table 45 and Table 46 - Table 51 showing selected baseline characteristics by cohort and country). The substantial difference in the mean age of the Hungarian study population may account for differences in outcome frequencies observed in Hungary.

The mean BMI of the study participants is similar between cohorts, with 23.5 for DNG, 24.6 for OAED and 23.3 for NAED and 23.5 for the study population as the whole. The BMI profiles for the (sub-) cohorts are shown in Table 11. There were no substantial differences in mean BMI between the countries: Germany 24.1, Poland 22.7, Russia 24.2, Hungary 22.0, Switzerland 23.1 and Ukraine 24.8 (cf. Table 45 and Table 46 - Table 51).

The educational level attained by study participants was lower than university entrance level for 16.5% of the study participants, 36.9% had a university entrance level and 46.6% had a university degree. There were educational differences between the user cohorts, with a greater percentage of women in the OAED having higher than a university entrance level education compared to the other user cohorts (Table 11). This is probably a reflection of differences in age distribution and differences between countries. The proportion of women with a university degree varies from 61.2% in Russia to 14.9% in Germany. In the other countries, the percentages were as follows: Hungary (30.6%), Switzerland (31.1%), Poland (45.1%) and Ukraine (46.1%) (cf. Table 45 and Table 46 - Table 51).

The proportion of smokers (19.4%, 21.6% and 20.2% in DNG, OAED, NAED users, respectively) and heavy smokers, (>15 cigarettes/day) (3.0%, 8.3%, 2.7% in DNG, OAED, NAED users, respectively) is higher in the OAED cohort (Table 11). The proportion of smokers is lowest in Russia and Ukraine (15.7% and 15.3%, respectively) compared to Germany (32.9%), Switzerland (28.4%), Hungary (26.4%) and Poland (20.3%) (cf. Table 45 and Table 46 - Table 51).

Table 11: Demographic characteristics by (sub-)cohorts

	DNG	OAED			NAED			Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED		
Number (%) of women	3,023 (100%)	2,542 (100%)	829 (100%)	3,371 (100%)	16,638 (100%)	3,246 (100%)	20,016 (100%)	20 (100%)	26,430 (100%)
BMI (kg/m²)									
Mean (SD)	23.5 (4.39)	24.4 (4.16)	25.1 (5.26)	24.6 (4.46)	23 (4.02)	24.5 (4.51)	23.3 (4.17)	25.3 (5.22)	23.5 (4.26)
Median	22.5	24.2	24.3	24.2	22.2	23.8	22.5	24.4	22.7
BMI category									
< 20	573 (19.0%)	304 (12.0%)	109 (13.1%)	413 (12.3%)	3,622 (21.8%)	343 (10.6%)	3,976 (19.9%)	2 (10.0%)	4,964 (18.8%)
>= 20 and <25	1,571 (52.0%)	1,174 (46.2%)	347 (41.9%)	1,521 (45.1%)	8,637 (51.9%)	1,610 (49.6%)	10,293 (51.4%)	8 (40.0%)	13,393 (50.7%)
>= 25 and <30	608 (20.1%)	855 (33.6%)	250 (30.2%)	1,105 (32.8%)	3,337 (20.1%)	992 (30.6%)	4,368 (21.8%)	6 (30.0%)	6,087 (23.0%)
>= 30 and <35	200 (6.6%)	152 (6.0%)	85 (10.3%)	237 (7.0%)	826 (5.0%)	215 (6.6%)	1,065 (5.3%)	2 (10.0%)	1,504 (5.7%)
>= 35	69 (2.3%)	57 (2.2%)	38 (4.6%)	95 (2.8%)	212 (1.3%)	84 (2.6%)	308 (1.5%)	2 (10.0%)	474 (1.8%)
Missing	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.0%)	2 (0.1%)	6 (0.0%)	0 (0.0%)	8 (0.0%)
Educational level									
Lower than university entrance level	654 (21.6%)	197 (7.7%)	52 (6.3%)	249 (7.4%)	3,090 (18.6%)	365 (11.2%)	3,466 (17.3%)	2 (10.0%)	4,371 (16.5%)
Univerity entrance level	1,006 (33.3%)	698 (27.5%)	466 (56.2%)	1,164 (34.5%)	6,243 (37.5%)	1,267 (39.0%)	7,572 (37.8%)	13 (65.0%)	9,755 (36.9%)
Higher than university entrance level	1,363 (45.1%)	1,647 (64.8%)	311 (37.5%)	1,958 (58.1%)	7,305 (43.9%)	1,614 (49.7%)	8,978 (44.9%)	5 (25.0%)	12,304 (46.6%)
Current smoker	587 (19.4%)	524 (20.6%)	205 (24.7%)	729 (21.6%)	3,473 (20.9%)	556 (17.1%)	4,049 (20.2%)	6 (30.0%)	5,371 (20.3%)
Thereof									
Heavy smoker (>15 cigarettes / day)	91 (3.0%)	215 (8.5%)	66 (8.0%)	281 (8.3%)	424 (2.5%)	119 (3.7%)	547 (2.7%)	0 (0.0%)	919 (3.5%)

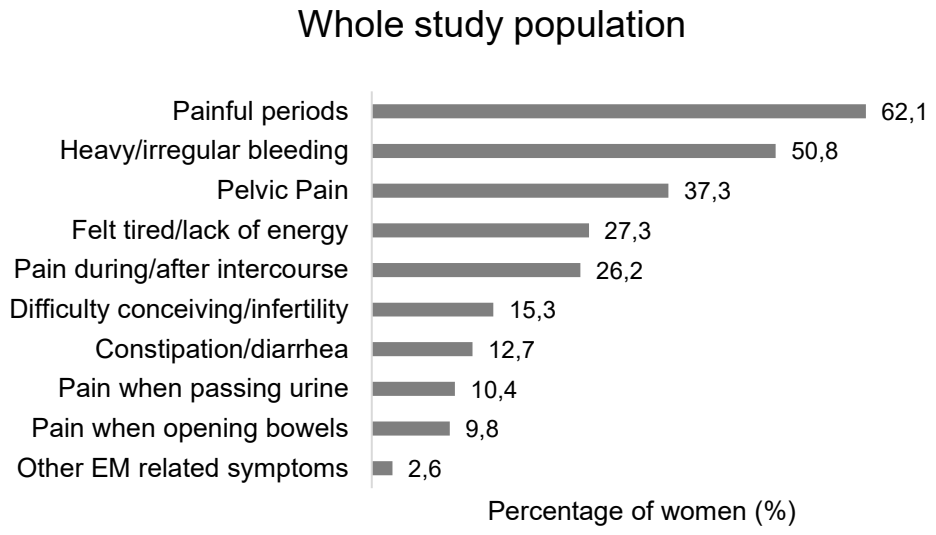
Gynecological history parameters such as age at menarche, mean number of live births and number of miscarriages/abortion and stillbirths are almost identical. There is a substantial difference in the proportion of women who have previously been pregnant; it is much smaller in the NAED cohort compared to the other two cohorts. This difference can also be attributed to the differences in the age distribution (Table 12).

Table 12: Age at menarche, pregnancy status and number of live births, miscarriages, stillbirths or abortions at study entry

	DNG	OAED			NAED			Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED		
Number (%) of women	3,023 (100%)	2,542 (100%)	829 (100%)	3,371 (100%)	16,638 (100%)	3,246 (100%)	20,016 (100%)	20 (100%)	26,430 (100%)
Age at menarche (years)									
Mean (SD)	13 (1.34)	12.7 (1.33)	13.2 (1.46)	12.8 (1.37)	12.9 (1.30)	12.7 (1.41)	12.8 (1.32)	13.1 (1.37)	12.9 (1.33)
Gravidity	1,936 (64.0%)	1,494 (58.8%)	661 (79.7%)	2,155 (63.9%)	8,177 (49.1%)	2,090 (64.4%)	10,390 (51.9%)	17 (85.0%)	14,498 (54.9%)
Parity	1,785 (59.0%)	1,403 (55.2%)	645 (77.8%)	2,048 (60.8%)	7,378 (44.3%)	2,017 (62.1%)	9,511 (47.5%)	15 (75.0%)	13,359 (50.5%)
Number of live births									
Mean (SD)	1.5 (0.66)	1.5 (0.66)	1.6 (0.74)	1.5 (0.69)	1.5 (0.63)	1.6 (0.78)	1.5 (0.67)	1.8 (0.86)	1.5 (0.67)
Number of miscarriages, still births, abortions									
Mean (SD)	2 (1.35)	2 (1.38)	2.3 (1.44)	2.1 (1.41)	2 (1.31)	2.2 (1.56)	2 (1.37)	3.1 (2.2)	2 (1.38)

At baseline, the women were asked to report their endometriosis-related symptoms. For all study participants, the most frequently reported symptom was pain during menstruation (62.1%), followed by heavy and/or irregular periods (50.8%) as shown in Figure 3.

Figure 3: Endometriosis-associated symptoms



The most pronounced differences regarding endometriosis-associated symptoms are in relation to pelvic pain (reported by 51.5% of the DNG users, 57.0% of the OAED users but only 31.8% of the

NAED users) and difficulty conceiving/infertility (22.7% of the DNG users, 25.5% of the OAED users but only 12.4% of the NAED users). DNG users more frequently suffer from problems associated with digestion (constipation/diarrhea) than OAED users (21.1 % vs. 19.4%), while OAED users tend to have more problems with pelvic pain (57.0%), heavy or irregular bleeding (50.5%) and infertility/difficulties conceiving (25.5%) compared to DNG users (51.5%, 47.3%, and 22.7%, respectively).

Table 13: Endometriosis-associated symptoms at study entry

	DNG	OAED			NAED				Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	Other NAED	All NAED	
Painful periods	67.3%	62.9%	80.9%	67.3%	61.8%	54.2%	38.6%	60.4%	62.1%
Heavy/irregular bleeding	47.3%	44.1%	70.3%	50.5%	51.2%	51.1%	61.4%	51.3%	50.8%
Pelvic Pain	51.5%	52.3%	71.7%	57.0%	29.3%	44.5%	34.1%	31.8%	37.3%
Felt tired/lack of energy	44.0%	32.3%	21.5%	29.6%	23.1%	29.9%	42.4%	24.4%	27.3%
Pain during/after intercourse	38.5%	37.4%	52.4%	41.1%	19.3%	35.5%	16.7%	21.9%	26.2%
Difficulty conceiving/infertility	22.7%	26.5%	22.4%	25.5%	9.9%	25.5%	6.8%	12.4%	15.3%
Constipation/diarrhea	21.1%	21.2%	13.9%	19.4%	9.1%	15.3%	24.2%	10.2%	12.7%
Pain when passing urine	11.2%	18.4%	7.4%	15.7%	7.1%	21.2%	14.4%	9.5%	10.4%
Pain when opening bowels	13.7%	16.7%	8.8%	14.8%	6.0%	19.9%	12.9%	8.3%	9.8%
Other EM related symptoms	6.1%	2.2%	4.1%	2.7%	2.0%	1.9%	3.0%	2.0%	2.6%

There were differences between the countries in relation to the endometriosis-related symptoms reported by the women as shown in Table 14.

Table 14: Endometriosis-associated symptoms by country

	Germany	Poland	Russia	Hungary	Switzerland	Ukraine	Total
Painful periods	74.0%	70.3%	64.0%	52.5%	79.7%	72.3%	62.1%
Heavy/irregular bleeding	43.2%	55.4%	49.1%	51.0%	46.0%	62.6%	50.8%
Pelvic Pain	44.8%	54.5%	41.0%	21.0%	54.1%	60.8%	37.3%
Felt tired/lack of energy	30.0%	41.5%	25.0%	24.8%	58.1%	39.6%	27.3%
Pain during/after intercourse	27.9%	35.1%	29.9%	14.6%	59.5%	41.0%	26.2%
Difficulty conceiving/infertility	12.5%	14.9%	21.9%	4.4%	24.3%	19.0%	15.3%
Constipation/diarrhea	15.4%	24.3%	11.7%	10.3%	43.2%	18.5%	12.7%

	Germany	Poland	Russia	Hungary	Switzerland	Ukraine	Total
Pain when passing urine	8.2%	11.3%	15.0%	4.7%	21.6%	6.4%	10.4%
Pain when opening bowels	12.5%	14.2%	13.9%	2.4%	39.2%	8.3%	9.8%
Other EM related symptoms	6.0%	6.8%	0.8%	3.7%	23.0%	3.8%	2.6%

At study entry, the participants were asked to rate their endometriosis-related pain in the preceding four weeks, with 0 being no pain and 10 being unbearable pain.

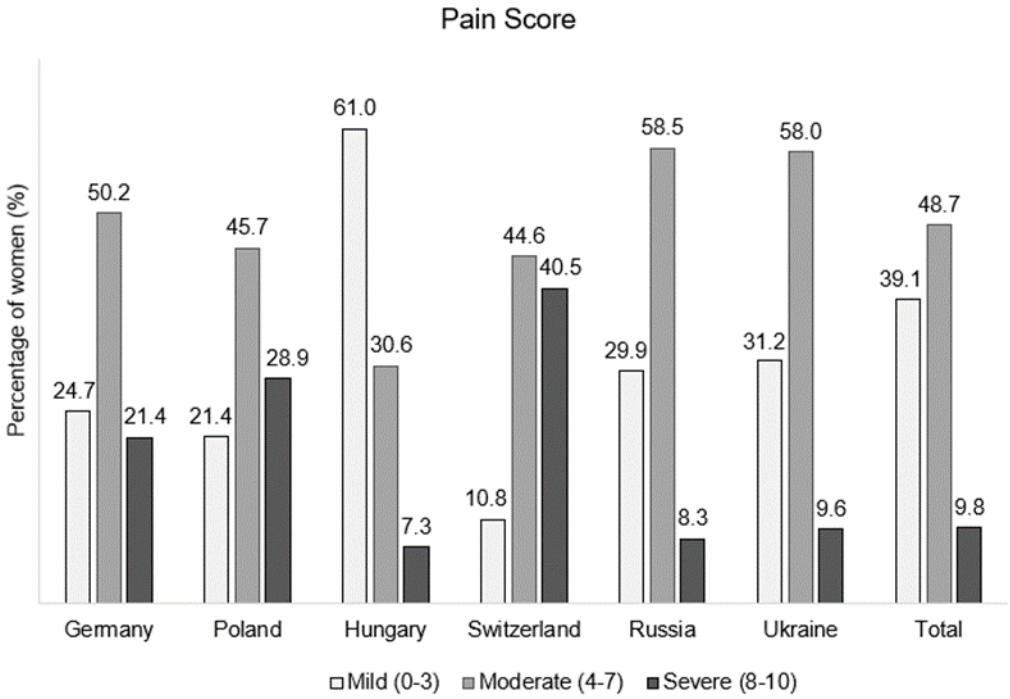
The proportion of women reporting severe pain is highest among the DNG users with 19.0% compared to 13.8% among the GnRH-a users and 11.7% among the Danazol users. In contrast, severe pain was perceived by 7.8% of the NAED users (Table 15).

Table 15: Severity of endometriosis-associated pain by (sub-)cohorts

	DNG	OAED			NAED			Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED		
Number (%) of women	3,023 (100%)	2,542 (100%)	829 (100%)	3,371 (100%)	16,638 (100%)	3,246 (100%)	20,016 (100%)	20 (100%)	26,430 (100%)
Severity of pain									
Missing	137 (4.4%)	82 (3.2%)	6 (0.7%)	88 (2.6%)	329 (1.9%)	93 (2.9%)	435 (2.2%)	0 (0.0%)	660 (2.5%)
mild (0-3)	849 (28.1%)	660 (26.0%)	88 (10.6%)	748 (22.2%)	7,605 (45.7%)	1,057 (32.6%)	8,722 (43.6%)	3 (15%)	10,322 (39.1%)
moderate (4-7)	1,462 (48.4%)	1,450 (57.0%)	638 (77.0%)	2.088 (61.9%)	7,389 (44.4%)	1,857 (57.2%)	9.296 (46.4%)	16 (80.0%)	12,862 (48.7%)
severe (8-10)	575 (19.0%)	350 (13.8%)	97 (11.7%)	447 (13.3%)	1.315 (7.9%)	239 (7.4%)	1.563 (7.8%)	1 (5.0%)	2.586 (9.8%)

The perception of endometriosis-associated pain differed between the countries as shown in Figure 4. The proportion of Hungarian, Russian and Ukrainian study participants reporting severe pain is much lower (7.3%, 8.3%, and 9.6%, respectively) than among women in Switzerland (40.5%), Poland (28.9%) and Germany (21.4%)

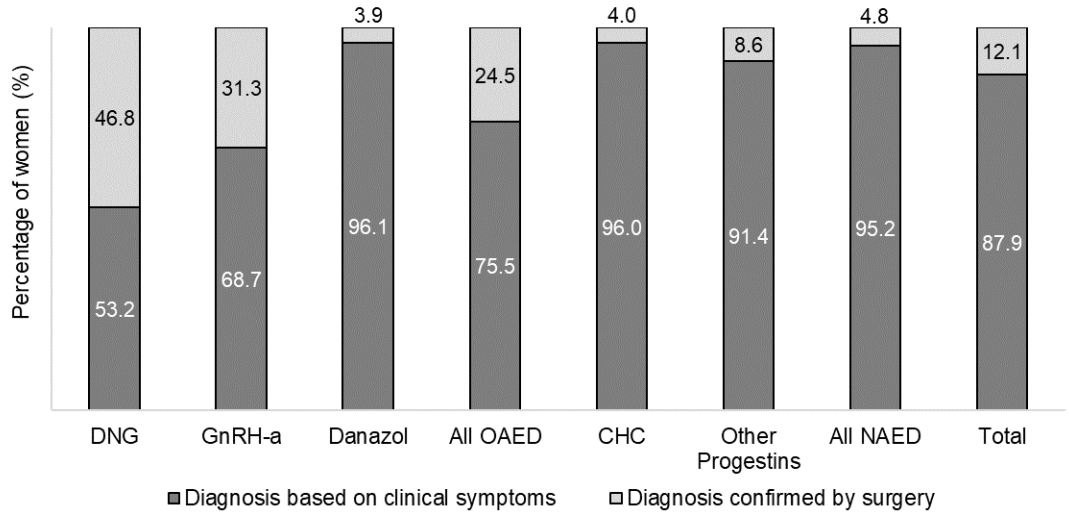
Figure 4: Severity of endometriosis-associated pain by country



The physicians who recruited participants for the VIPOS study were requested to classify their patients' diagnosis of endometriosis into surgically/laparoscopically confirmed or based on clinical symptoms.

Overall 87.9% of the study participants were diagnosed with endometriosis based on their clinical symptoms, and 12.1% of the overall population received a surgical diagnosis. There are pronounced differences between the (sub-)cohorts. A higher percentage of the endometriosis diagnoses of DNG and GnRH-a users were confirmed by surgery/laparoscopy: 46.8% (DNG) and 31.3% (GnRH-a), compared to less than 5% of all NAED users. The other endometriosis diagnoses were based on clinical symptoms as shown in Figure 5 (numbers cf. Table 52).

Figure 5: Classification of endometriosis diagnosed by (sub-)cohorts



The higher proportion of surgically confirmed endometriosis in DNG users compared to the GnRH-a users reflects the differences in diagnostic methods in the participating countries. In Russia and Ukraine, and to a lesser extent in Poland, the percentage of surgically confirmed cases of endometriosis is quite low but there are no substantial differences between the DNG and OAED users.[13] (cf. Table 53 - Table 58). In users of NAED, the endometriosis diagnosis is based primarily on clinical symptoms in all countries.

Data on personal medical history were also collected at baseline. The distribution of selected diseases is shown in Table 16. The percentage of women with a treated depression is the highest in the DNG cohort with 5.3% compared to GnRH-a (1.5%), Danazol (0.2%), Other progestins (3.2%) and CHC (1.9%). The prevalence of treated anemia is also higher in the DNG cohort (6.5%) in comparison to the other (sub-)cohorts, with the exception of the Other progestin users with a proportion of 8.2%.

A personal history of other serious diseases was more frequently reported by DNG users (4.8%) compared to OAED (1.7%) and NAED users (2.2%). Moreover, DNG users were more likely to report having undergone surgery not related to endometriosis at some point prior to study entry (29.0%) compared to 14.2% of the OAED and 14.5% of the NAED users. This could indicate that the DNG users are in a worse general health condition than the users of the other (sub-)cohorts.

[13] The baseline questionnaire did not contain a question regarding imaging procedures supporting the endometriosis diagnosis. The Ukrainian physicians added manually for more than 30% of their patients that the diagnosis was not only based on clinical symptoms but also on ultrasound. A few physicians also reported that (clinical) diagnosis was confirmed by MRT.

Table 16: Personal history of selected diseases by (sub-)cohorts

	DNG	OAED			NAED			Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED		
Number (%) of women	3,023 (100%)	2,542 (100%)	829 (100%)	3,371 (100%)	16,638 (100%)	3,246 (100%)	20,016 (100%)	20 (100%)	26,430 (100%)
Depression*	159 (5.3%)	39 (1.5%)	2 (0.2%)	41 (1.2%)	318 (1.9%)	103 (3.2%)	423 (2.1%)	1 (5.0%)	624 (2.4%)
Anemia*	196 (6.5%)	103 (4.1%)	12 (1.4%)	115 (3.4%)	899 (5.4%)	266 (8.2%)	1,174 (5.9%)	2 (10.0%)	1,487 (5.6%)
Myocardial infarction*	2 (0.1%)	2 (0.1%)	0 (0.0%)	2 (0.1%)	2 (0.0%)	1 (0.0%)	3 (0.0%)	0 (0.0%)	7 (0.0%)
Stroke*	3 (0.1%)	7 (0.3%)	1 (0.1%)	8 (0.2%)	8 (0.0%)	6 (0.2%)	14 (0.1%)	0 (0.0%)	25 (0.1%)
Clotting lung (pulmonary embolism)*	3 (0.1%)	3 (0.1%)	0 (0.0%)	3 (0.1%)	1 (0.0%)	2 (0.1%)	3 (0.0%)	0 (0.0%)	9 (0.0%)
Deep venous thrombosis*	23 (0.8%)	14 (0.6%)	1 (0.1%)	15 (0.4%)	20 (0.1%)	24 (0.7%)	45 (0.2%)	0 (0.0%)	83 (0.3%)
Cancer*	15 (0.5%)	10 (0.4%)	0 (0.0%)	10 (0.3%)	30 (0.2%)	13 (0.4%)	43 (0.2%)	0 (0.0%)	68 (0.3%)
Other serious diseases*	146 (4.8%)	51 (2.0%)	5 (0.6%)	56 (1.7%)	349 (2.1%)	92 (2.8%)	446 (2.2%)	0 (0.0%)	648 (2.5%)
Any none endometriosis related surgery	877 (29.0%)	380 (14.9%)	100 (12.1%)	480 (14.2%)	2,402 (14.4%)	477 (14.7%)	2,908 (14.5%)	5 (25.0%)	4,270 (16.2%)

Note: * treated by HCP only

The proportions of selected risk factors are shown in Table 17. A family history of depression is more frequently reported by users of Other progestins (14.4%) compared to the DNG (9.4%), GnRH-a (6.1%) or CHC (8.3) users. A higher proportion of Other progestins users had a family history of endometriosis (20.2%) compared to 18.8% of CHC, 13.1% of DNG and 11.2% of GnRH-a users. The highest percentage of family history of VTE is also reported by users of Other progestins (16.8%) followed by DNG users with 10.3%.

Table 17: Selected risk factors by (sub-)cohorts

	DNG	OAED			NAED			Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED		
Number (%) of women	3,023 (100%)	2,542 (100%)	829 (100%)	3,371 (100%)	16,638 (100%)	3,246 (100%)	20,016 (100%)	20 (100%)	26,430 (100%)
Endometriosis of relatives	397 (13.1%)	285 (11.2%)	36 (4.3%)	321 (9.5%)	3,132 (18.8%)	657 (20.2%)	3,807 (19.0%)	1 (5.0%)	4,526 (17.1%)
Depression of relatives	285 (9.4%)	154 (6.1%)	13 (1.6%)	167 (5.0%)	1,382 (8.3%)	466 (14.4%)	1,854 (9.3%)	1 (5.0%)	2,307 (8.7%)
Thrombosis or pulmonary embolism of relatives	311 (10.3%)	177 (7.0%)	15 (1.8%)	192 (5.7%)	1,210 (7.3%)	545 (16.8%)	1,772 (8.9%)	1 (5.0%)	2,276 (8.6%)
BMI >=25 to <30	608 (20.1%)	855 (33.6%)	250 (30.2%)	1,105 (32.8%)	3,337 (20.1%)	992 (30.6%)	4,368 (21.8%)	6 (30.0%)	6,087 (23.0%)
BMI >=30 to <35	200 (6.6%)	152 (6.0%)	85 (10.3%)	237 (7.0%)	826 (5.0%)	215 (6.6%)	1,065 (5.3%)	2 (10.0%)	1,504 (5.7%)
BMI >=35	69 (2.3%)	57 (2.2%)	38 (4.6%)	95 (2.8%)	212 (1.3%)	84 (2.6%)	308 (1.5%)	2 (10.0%)	474 (1.8%)
Smoker	587 (19.4%)	524 (20.6%)	205 (24.7%)	729 (21.6%)	3,473 (20.9%)	556 (17.1%)	4,049 (20.2%)	6 (30.0%)	5,371 (20.3%)
Heavy smoker (>15 cigarettes / day)	91 (3.0%)	215 (8.5%)	66 (8.0%)	281 (8.3%)	424 (2.5%)	119 (3.7%)	547 (2.7%)	0 (0.0%)	919 (3.5%)

A secondary objective of the VIPOS study was to investigate the risks of short- and long-term use of DNG and of established endometriosis treatments in adolescent women. Adolescents comprise less than 3% of the AT study population. However, because most adolescents were treated with NAED, they constitute 3.0% of the NAED cohort. In contrast, only 0.3% of DNG users and 0.1% of OAED users were below the age of 18 years (Table 18). Therefore, the risk posed to adolescents by

short- and long-term use of DNG and the other treatment groups cannot be analyzed with the data of the VIPOS study.

Table 18: Adolescents by (sub-)cohorts

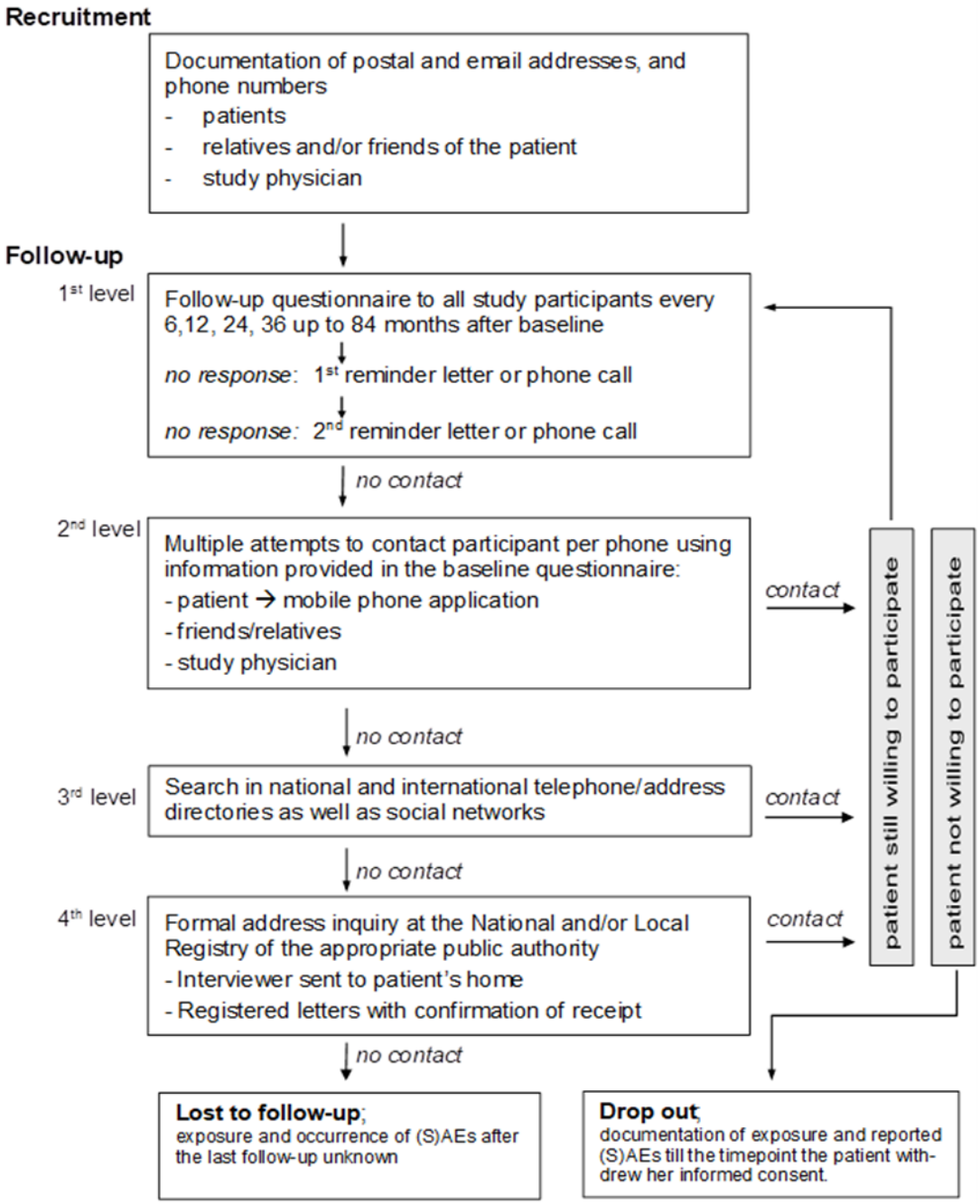
	DNG	OAED			NAED			Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED		
Number (%) of women	3,023 (100%)	2,542 (100%)	829 (100%)	3,371 (100%)	16,638 (100%)	3,246 (100%)	20,016 (100%)	20 (100%)	26,430 (100%)
Adolescents <18 years	10 (0.3%)	2 (0.1%)	2 (0.2%)	4 (0.1%)	593 (3.6%)	11 (0.3%)	604 (3.0%)	0 (0.0%)	618 (2.3%)

10.2 Outcome data

10.2.1 Loss to Follow-up

A low lost to follow-up rate was important for the success of the study and in order to minimize it, a multi-faceted, four-level follow-up process was utilized in the VIPOS study (Figure 6).

Figure 6: Cascade of activities to obtain patient-related follow-up information



Level one activities included mailing the follow-up questionnaire and if there was no response, one or two reminder letters. In Russia and Ukraine, follow-up was conducted via CATI. If study participants had not been reached by telephone within the first month, further attempts were made to reach them for at least another four months. If Level one activities did not lead to a response, multiple attempts were made via telephone to contact the woman and/or the additional contacts (that is the friends or relatives she named on the informed consent form) as well as the recruiting gynecologist. In Russia, a mobile (cell) phone application was implemented to allow the opportunity of completing the follow-up questionnaire via mobile phone or home computer. The study participants received short text messages asking them to complete the survey and emphasizing the importance of each woman's response. In parallel to these Level two activities, searches in national telephone and address directories, as well as social networks, were started (Level three activities). If this was not successful, an official address search via the respective citizen registry was conducted where possible. Otherwise, interviewers were sent to the patient's home or registered letters with confirmation of receipt were sent via postal mail.

Despite the extensive efforts made to conduct these activities, the overall lost-to-follow-up rate of 16.8% was higher than the 5% rate estimated in 2010 (which had been based on populations of oral contraceptive users in the EURAS OC/LASS studies). However, the study population of women with endometriosis differed more from users of oral contraceptives than originally expected. For example, a greater number of women than anticipated refused to take part in a long-term follow-up of more than five years and were not willing to provide their new contact details when they moved. The study physicians were unable to provide updated contacted details for their patients because quite frequently the women changed gynecologists or had visited the specialized endometriosis center at study entry only. Moreover, increased sensitivity to data protection issues resulted in many women blocking address inquiries.

Importantly, however, the lost-to-follow-up rates between the user cohorts did not differ substantially: 15.6% for DNG, 17.5% for OAED and 16.9% for the NAED cohort. If the loss-to-follow rate affected the results of the study, each user cohort would be impacted in a similar way.

10.2.2 Validation of self-reported anemia

Details of the validation process were described in Section 9.12. Many anemia cases self-reported by study participants did not meet the *a priori* criteria to be verified as a "confirmed" outcome of interest. Anemia cases were considered confirmed if diagnosed by a physician (for example based on hemoglobin value), did not have an obvious alternative explanation (for example gastrointestinal bleeding, post-surgical, dietary, pregnancy and/or delivery related) and had a pertinent treatment. Treatment with iron tablets, treatment with iron infusions/injections and treatment with blood transfusions were categories for the severity of the anemia.

Table 59 shows a detailed listing of the self-reported anemia cases. The question "Have you been diagnosed with anemia" was checked with "Yes" on the follow-up questionnaire a total of 958 times during the follow-up periods (=self-reported) by 793 women. Overall, 197 cases (21%) were confirmed. These represented first-ever or a deterioration of a pre-existing anemia. The number of confirmed cases is equal to the number of women with a confirmed anemia. Confirmed cases at each follow-up were included in the highest possible treatment category. For example, an anemia

requiring treatment with both iron tablets and subsequently iron injections was included within the iron injections/infusions category only.

A total of 761 self-reported cases were not confirmed (79%). This group breaks down into six sub-groups as follows:

1. Recurrent anemia

   Events reported where the woman had a prior anemia event confirmed and there had been no change in her condition.

2. Potential Anemia

   These are events that do not represent anemia according to the criteria described in Section 9.12. In some cases, it was not possible to obtain the needed comprehensive information for a case assessment (either the woman and/or the attending physician was unable, or refused, to provide the necessary diagnostic information). These cases were unanimously classified by the blinded adjudicators (cf. Section 9.13) as not anemia, based on the available information.

3. Anemia caused by other reason

   According to the study definition, only endometriosis-related anemia are outcomes of interest. Therefore, anemia secondary to other diseases or causes were classified as not confirmed (for example anemia secondary to primary diseases like colitis ulcerosa, secondary to surgery, trauma or dietary habits and – in case of Ex-users - occurring during pregnancy or delivery).

4. Anemia not confirmed by diagnostic measures

   These were events where the diagnostic tests and clinical case information provided by the study participant and/or her treating physician did not meet the criteria for anemia. As such, these cases are probably not anemia. As these cases were also unanimously classified by the blinded adjudicators (cf. Section 9.13) as not anemia, the risk of misclassification seems low.

5. Anemia not treated by HCP

   Self-reported events where the woman did not attend an HCP for treatment or diagnosis (that is self-diagnosed, self-treatment, self-reported event)

6. No event

   These are reports that do not present any (new) adverse event:

   a) reports of events that had already occurred before study entry

   b) reports of events that occurred during the study period but were already reported in a previous follow-up

   c) misunderstanding of the question/inadvertently ticked box in the questionnaire

The overall incidence rate of confirmed, medically relevant, newly diagnosed anemia (first-ever or a deterioration of a pre-existing anemia) was 23.4 events per 10,000 WY. This was markedly lower than predicted. Based on the available literature, it was assumed a background prevalence of anemia in premenopausal European women of 10-15% and an anemia incidence of 100 events per 10,000 WY (cf. Section 9.8). If the first, second and third sub-groups (potential anemia, recurrent

anemia, and anemia caused by other reasons) were included in the analysis, the incidence rate increased to 84.3 cases per 10,000 WY. This rate approaches the rate assumed during protocol development (100 events per 10,000 WY).

10.2.3 Validation of self-reported depression

Details of the validation process were described in Section 9.12.

Many depression cases self-reported by study participants did not meet the a priori criteria to be verified as a "confirmed" outcome of interest. Depression cases were considered confirmed if they have been diagnosed by a psychiatrist or a physician specialized in psychiatry. Outpatient treatment (=treated by a psychiatrist), hospital admission and/or (attempted) suicide were categories for the severity of the depression. Patients with a previously diagnosed depression (before the start of treatment) could only be considered as confirmed cases if they experienced a significant deterioration in their condition (for example first-time suicide attempt).

Table 60 shows a detailed listing of the self-reported depression cases.
The question "Have you been diagnosed with a depression requiring treatment" was checked with "Yes" on the follow-up questionnaire a total of 961 times during the follow-up periods (=self-reported) by 700 women. Overall, 139 cases (15%) were confirmed.
These depressions were reported by 138 women. One study participant in the "Ex-use" cohort had a first depressive episode which was treated by a psychiatrist and attempted later during the study period to commit suicide which was classified as worsening of the pre-existing depression. Both events occurred when she had stopped EMT use for more than three months and are counted in the Ex-use cohort.

Confirmed cases at each follow-up timepoint were included in the highest possible treatment category. For example, if a woman was first treated by a psychiatrist and then subsequently admitted to hospital, the case was included within the "hospital admission" category only.

A total of 822 self-reported cases were not confirmed (85%). This group breaks down into seven sub-groups as follows:

1. Recurrent depression
   Events reported by women with a (pre)-existing depression without changes in her condition.

2. Potential depression
   These are events that do not represent depression according to the criteria described in Section 9.12. In some cases, it was not possible to obtain the needed comprehensive information for a case assessment (either the woman and/or the attending physician was unable, or refused, to provide the necessary diagnostic information. These cases were unanimously not classified by the blinded adjudicators (cf. Section 9.13) like depression, based on the available information.

3. Depression treated by a general practitioner
   According to the study definition, only cases treated at least by a psychiatrist or a physician specialized in psychiatry were considered as confirmed. Depression treated by a general practitioner – with or without antidepressants – remained therefore as not confirmed.

4. Depressive disorders treated by a psychologist
   Events reported as depression but treated by a psychologist (non-medical doctor) with counseling, talking therapy, just to name a few.

5. Other psychiatric disorders
   Events classified as bipolar or anxiety disorders (including panic attacks), schizophrenia[14], eating disorders (bulimia) or burnout syndrome did not classify for the study definition for a confirmed depression and were combined here.

6. Other psychiatric/mental problems
   This category of not confirmed cases combines cases of self-reported depression where the woman did not attend an HCP for treatment or diagnosis or if when she went to see a doctor another medical condition (for example, depressive mood) was diagnosed.

7. No event
   These are reports that do not present any (new) adverse event:
   a) reports of events that had already occurred before study entry
   b) reports of events that occurred during the study period but were already reported in a previous follow-up
   c) misunderstanding of the question/inadvertently ticked box in the questionnaire

The overall incidence rate of confirmed, clinically relevant depression (newly diagnosed or worsening of a pre-existing depression) was 16.5 events per 10,000 WY. This is markedly lower than predicted. The expected incidence rate for newly diagnosed or worsening depression was 100 events in 10,000 WY based on an estimated prevalence rate of 20% for depression in women with endometriosis (cf. Section 9.8).
The Safety monitoring and Advisory Council suggested several sensitivity analyses which also included potential depressions and depression treated by general practitioners with antidepressants (cf. Section 10.3.2).

10.2.4 Treatment discontinuation

The study participants were asked to record their use of endometriosis medication in each follow-up questionnaire. If they stopped or switched their EMT, they were asked about their reasons for stopping or switching and were offered the following pre-defined options: (1) Trying to become pregnant; (2) Treatment duration finished; (3) Medication ineffective; (4) Side effects of medication, if yes, which; (5) Other reason, if yes, which. Women could provide multiple answers.

Treatment discontinuation due to ineffective medication and/or side effects were defined as treatment failure (one of the primary outcomes, cf. Section 10.3.3). In contrast to the other primary outcomes, the information provided by the women in relation to side effects or ineffectiveness was not validated with the attending gynecologists. If the woman provided specific information about the side effects or explained in more detail the other reasons for stopping/switching the EMT, her responses were coded in order to categorize them. Before doing so, the answers were checked for

[14] Bipolar disorders and schizoaffective disorders were excluded by request of the Safety Monitoring and Advisory Council.

consistency. For example, if a woman specified that she stopped because "the advised treatment duration was over" but she had not checked the appropriate box, the "Treatment duration finished" option was set to yes. If personal reasons (for example "medication too expensive") were provided as side effects, the answer was allocated to the other reasons and not counted as a side effect.

Treatment discontinuation is shown as incidence proportion per 100 treatment starts (cf. Section 9.10 "Statistical methods").

All the reasons for treatment discontinuation are displayed in Table 19.

Table 19: Treatment discontinuation due to treatment failure and due to other reasons: Number of treatment starts, number of reasons for treatment failure and incidence proportions per 100 treatment starts by the user (sub-)cohort

	DNG	OAED			NAED			Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED	
Number of treatment starts	4,137	2,831	1,170	4,001	28,074	5,559	34,204	42,342
Treatment failure								
N	**668**	**148**	**55**	**203**	**3,244**	**554**	**3,862**	**4,733**
*IP **	**16.1**	**5.2**	**4.7**	**5.1**	**11.6**	**10.0**	**11.3**	**11.2**
(95% CI)	**(15.0-17.3)**	**(4.4-6.1)**	**(3.6-6.1)**	**(4.4-5.8)**	**(11.2-11.9)**	**(9.2-10.8)**	**(11.0-11.6)**	**(10.9-11.5)**
*Thereof ***								
	144	40	19	59	406	140	560	763
Medication	3.5	1.4	1.6	1.5	1.4	2.5	1.6	1.8
ineffective	(2.9-4.1)	(1.0-1.9)	(0.98-2.5)	(1.1-1.9)	(1.3-1.6)	(2.1-3.0)	(1.5-1.8)	(1.7-1.9)
	558	116	36	152	2,895	440	3,387	4,097
	13.5	4.1	3.1	3.8	10.3	7.9	9.9	9.7
Side effects	(12.5-14.6)	(3.4-4.9)	(2.2-4.2)	(3.2-4.4)	(10.0-10.7)	(7.2-8.7)	(9.6-10.2)	(9.4-10.0)
Treatment discontinuation unrelated to treatment failure								
N	**2,293**	**1,800**	**836**	**2,636**	**14,574**	**2,850**	**17,723**	**22,652**
*IP **	**55.4**	**63.6**	**71.5**	**65.9**	**51.9**	**51.3**	**51.8**	**53.5**
(95% CI)	**(53.9-56.9)**	**(61.8-65.4)**	**(68.8-74.0)**	**(64.4-67.4)**	**(51.3-52.5)**	**(49.9-52.6)**	**(51.3-52.3)**	**(53.0-54.0)**
*Thereof ***								
	281	130	62	192	1,911	250	2,177	2,650
Trying to become pregnant	6.8	4.6	5.3	4.8	6.8	4.5	6.4	6.3
	(6.0-7.6)	(3.9-5.4)	(4.1-6.7)	(4.2-5.5)	(6.5-7.1)	(4.0-5.1)	(6.1-6.6)	(6.0-6.5)
	1,155	1,368	414	1,782	4,363	1,477	5,995	8,932
Treatment duration finished	27.9	48.3	35.4	44.5	15.5	26.6	17.5	21.1
	(26.6-29.3)	(46.5-50.2)	(32.6-38.2)	(43.0-46.1)	(15.1-16.0)	(25.4-27.8)	(17.1-17.9)	(20.7-21.5)
	938	364	382	746	8,585	1,198	9,921	11,605
	22.7	12.9	32.6	18.6	30.6	21.6	29.0	27.4
Other ***	(21.4-24.0)	(11.6-14.1)	(30.0-35.4)	(17.4-19.9)	(30.0-31.1)	(20.5-22.7)	(28.5-29.5)	(27.0-27.8)

*Note: * Incidence proportion is shown per 100 treatment starts.*
*Note. ** Multiple responses were possible.*
*Note: ** *Other patient-reported reasons for treatment discontinuation might include, for example, a resolution of current complaints, adherence to a physician's advice, planned hospitalization or surgery.*

The overall incidence proportion for treatment discontinuation due to reasons unrelated to treatment failure was much higher with 53.5 (95% CI 53.0-54.0) compared to the overall incidence proportion for treatment failure 11.2 (95% CI 10.9-11.5). The same was true for the incidence proportions of the individual (sub-)cohorts.

The incidence proportion for "Treatment duration finished" was highest in the GnRH-a sub cohort (48.3, 95%CI 46.5-50.2) for which a maximal treatment duration is clearly defined in the label. Due to their known, severe side effects, these medications were normally prescribed for 6 months or – with an add-back therapy - for a maximum of 12 months.
In the DNG cohort, this incidence proportion was 27.9 (95% CI, 26.6 - 29.3).

The subjectively perceived side effects most frequently reported by DNG users as the reason for discontinuation included bleeding problems, mood changes/depressive mood and weight problems. GnRH-a users most commonly reported mood changes/depressive mood, hot flushes and nausea/sickness. Danazol users most frequently reported nausea/sickness, blood pressure problems and weight problems as the side effects leading to treatment discontinuation. Bleeding problems comprised the most frequently reported side effect in all NAED (sub-)cohorts. CHC users also frequently suffered from weight problems and headache/migraine, users of Other progestins suffered from weight problems and mood changes/depressive mood.

Other patient-reported reasons for treatment discontinuation (reported in nearly all (sub-)cohorts) most commonly involved a resolution of current complaints, adherence to a physician's advice or simply a treatment break.

10.2.5 Serious adverse events

The main clinical outcomes in the VIPOS Study involved events associated with medically relevant anemia or depression. However, study participants were also asked to record on their follow-up questionnaires the occurrence of significant and/or serious adverse events including hospitalizations that occurred since they were last contacted. Data on fatalities were captured upon contact with relatives or health care professionals.

Serious adverse events (SAEs) 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 the said outcomes.

A total of 2,872 SAEs (341.1 SAE/10,000 WY, 95% CI 329.0-353.6) occurred among the VIPOS study participants, with the lowest incidence rate in the CHC users (260.6 SAE/10,000 WY, 95% CI 243.9-278.2) and the highest in Danazol users (546.5 SAE/10,000 WY, 95% CI 395.0-734.1). For the DNG users, an incidence rate of 401.6 SAE/10,000 WY, 95% CI 346.-463.3) was observed.

Table 61 shows the incidence rates of SAE by organ system (according to ICD10).

Thromboembolic events and fatalities were included in these numbers and are described in detail in Section 10.2.5.1 and Section 10.2.5.2.

Among the events of the cardiovascular system were three hemorrhagic strokes (two in Other progestin users and one in an Ex-user).

10.2.5.1 Thromboembolic events

As serious cardiovascular events, venous and arterial thromboembolic events were validated and classified as described in Section 9.12.

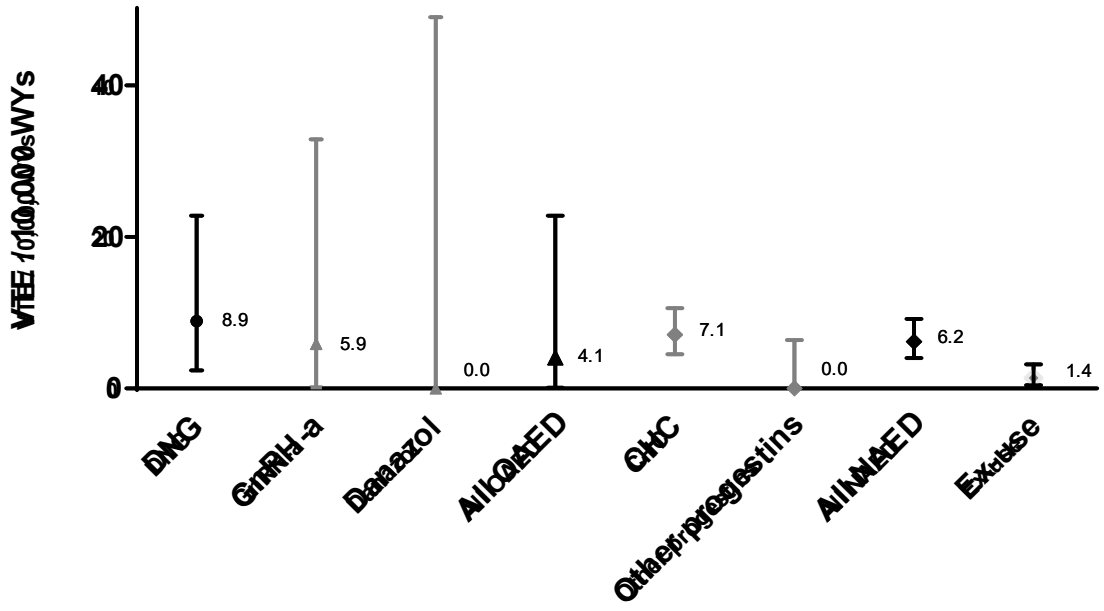
Overall, there were 35 confirmed VTE. The numbers of VTE and incidence rates by user (sub-) cohort were as follows:

- DNG (4 VTE; 8.9 VTE per 10,000 WY; 95% CI, 2.4-22.8),
- OAED (1 VTE; 4.1 VTE per 10,000 WY; 95% CI,0.1-22.8),
- NAED (25 VTE; 6.2 VTE per 10,000 WY; 95% CI, 4.0-9.2) and
- Ex-user (5 VTE; 1.4 VTE per 10,000 WY; 95% CI,0.4-3.2).

Most of the NAED cases occurred in users of CHC (24 VTE; 7.1 VTE per 10,000 WY; 95% CI,4.5-10.6). The incidence rates per 10,000 WY are graphically displayed in Figure 7.

There were no statistically significant differences in VTE risk between the main user cohorts (with a broad overlap of confidence intervals). The number of VTE events in the user cohorts were low (one VTE in the OAED cohort, four VTE in the DNG cohort); comparisons between user groups did not result in robust conclusions.

Figure 7: Venous thromboembolic events: Incidence rates per 10,000 WY (with 95% confidence intervals) per user (sub-) cohort



Numbers and incidence rates per 10,000 WY (with 95% confidence intervals) for all VTE and for pulmonary embolism events by (sub-)cohort are presented in Table 20.

Table 20: Venous thromboembolic events: Incidence rates per 10,000 WY (with 95% confidence intervals) by (sub-)cohort

	DNG	OAED			NAED			Ex-use	Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED			
Number of women	4,482	1,694	750	2,444	33,806	5,753	40,090	36,877	294	84,187
ALL VTE										
N	**4**	**1**	**0**	**1**	**24**	**0**	**25**	**5**	**0**	**35**
*IR **	**8.9**	**5.9**	**0.0**	**4.1**	**7.1**	**0.0**	**6.2**	**1.4**	**0.0**	**4.2**
(95% CI)	**(2.4-22.8)**	**(0.15-32.9)**	**(0.0-49.0)**	**(0.10-22.8)**	**(4.5-10.6)**	**(0.0-6.4)**	**(4.0-9.2)**	**(0.44-3.2)**	**(0.0-124.9)**	**(2.9-5.8)**
Thereof										
PE	1 2.2 (0.06-12.4)	1 5.9 (0.15-32.9)	0 0.0 (0.0-49.0)	1 4.1 (0.10-22.8)	10 3.0 (1.4-5.4)	0 0.0 (0.0-6.4)	10 2.5 (1.2-4.6)	1 0.27 (0.007-1.5)	0 0.0 (0.0-124.9)	13 1.5 (0.82-2.6)

Note: Incidence rate is shown per 10,000 WY*

The risk of VTE among users of hormonal medications is always of specific interest. Therefore, descriptions of all VTE cases under EMT exposure are presented in Annex 3.3.

Regarding arterial thromboembolic events (ATE), no increased risk was observed in DNG users. Of the 14 confirmed cases of ATE, none occurred in a DNG user. There were two acute myocardial infarctions (both Ex-users), 11 ischemic strokes (four NAED and seven Ex-users), and one transient ischemic attack (TIA) in an NAED user. The incidence rates per 10,000 WY (with 95% confidence intervals) for arterial thromboembolic events are shown in Table 21.

Table 21: Arterial thromboembolic events: Incidence rates per 10,000 WY (with 95% confidence intervals) per user (sub-)cohort

	DNG	OAED			NAED			Ex-use	Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED			
Number of women	4,482	1,694	750	2,444	33,806	5,753	40,090	36,877	294	84,187
All ATE										
N	**0**	**0**	**0**	**0**	**3**	**1**	**5**	**9**	**0**	**14**
*IR **	**0.0**	**0.0**	**0.0**	**0.0**	**0.89**	**1.7**	**1.2**	**2.4**	**0.0**	**1.7**
(95% CI)	**(0.0-8.2)**	**(0.0-21.8)**	**(0.0-49.0)**	**(0.0-15.1)**	**(0.18-2.6)**	**(0.04-9.7)**	**(0.40-2.9)**	**(1.1-4.6)**	**(0.0-124.9)**	**(0.91-2.8)**
Thereof										
AMI	0 0.0 (0.0-8.2)	0 0.0 (0.0-21.8)	0 0.0 (0.0-49.0)	0 0.0 (0.0-15.1)	0 0.0 (0.0-1.1)	0 0.0 (0.0-6.4)	0 0.0 (0.0-0.92)	2 0.54 (0.07-2.0)	0 0.0 (0.0-124.9)	2 0.24 (0.03-0.86)
Ischemic stroke	0 0.0 (0.0-8.2)	0 0.0 (0.0-21.8)	0 0.0 (0.0-49.0)	0 0.0 (0.0-15.1)	2 0.59 (0.07-2.1)	1 1.7 (0.04-9.7)	4 1.00 (0.27-2.6)	7 1.9 (0.76-3.9)	0 0.0 (0.0-124.9)	11 1.3 (0.65-2.3)
TIA	0 0.0 (0.0-8.2)	0 0.0 (0.0-21.8)	0 0.0 (0.0-49.0)	0 0.0 (0.0-15.1)	1 0.30 (0.007-1.6)	0 0.0 (0.0-6.4)	1 0.25 (0.006-1.4)	0 0.0 (0.0-1.0)	0 0.0 (0.0-124.9)	1 0.12 (0.003-0.66)

*Note: * Incidence rate is shown per 10,000 WY*

10.2.5.2 Fatal outcomes

Overall, 20 deaths were confirmed during the study period, one of which occurred in a DNG user[15] and one in an OAED user.

All fatalities were assessed for causality by the Safety Monitoring and Advisory Council who were blinded to endometriosis treatment exposure status. The SMAC deemed none of the cases causally related to an EMT.

In three cases, information on exposure to endometriosis treatment up until the time of death could not be obtained. These cases were accordingly categorized in the "allocation unknown" group. None of the fatalities in the "allocation unknown" group involved adolescents, although one woman had entered the study at the age of 16 (and died at the age of 18 due to a car accident).

The causes of death by user (sub-)cohort are summarized in Table 22. The most frequent cause of death was cancer: one NAED user with pancreatic cancer and eight Ex-users with breast cancer (three cases), lung cancer (two cases), gastric cancer (two cases) or cervical cancer (one case). In four cases, the cause of death remained unclear (despite having obtained death certificates in two of these cases[16]).

[15] The DNG user died from cerebral compression subsequent to known intracranial cyst with hemorrhage.

[16] The second page of a death certificate containing the cause of death is not provided to non-relatives.

Table 22: Fatalities by cause: Number and incidence per 10,000 WY (with 95% confidence intervals) by (sub-) cohort

	DNG	OAED			NAED			Ex-use	Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED			
Number of women	4,482	1,694	750	2,444	33,806	5,753	40,090	36,877	294	84,187
All deaths										
N	**1**	**1**	**0**	**1**	**4**	**0**	**4**	**11**	**3**	**20**
*IR **	**2.2**	**5.9**	**0.0**	**4.1**	**1.2**	**0.0**	**1.00**	**3.0**	**102.2**	**2.4**
(95% CI)	**(0.06-12.4)**	**(0.15-32.9)**	**(0.0-49.0)**	**(0.10-22.8)**	**(0.32-3.0)**	**(0.0-6.4)**	**(0.27-2.6)**	**(1.5-5.3)**	**(21.1-295.7)**	**(1.5-3.7)**
Reason										
Cancer	0 0.0 (0.0-8.2)	0 0.0 (0.0-21.8)	0 0.0 (0.0-49.0)	0 0.0 (0.0-15.1)	1 0.30 (0.007-1.6)	0 0.0 (0.0-6.4)	1 0.25 (0.006-1.4)	8 2.2 (0.94-4.3)	0 0.0 (0.0-124.9)	9 1.1 (0.49-2.0)
Accident	0 0.0 (0.0-8.2)	0 0.0 (0.0-21.8)	0 0.0 (0.0-49.0)	0 0.0 (0.0-15.1)	3 0.89 (0.18-2.6)	0 0.0 (0.0-6.4)	3 0.75 (0.15-2.2)	1 0.27 (0.007-1.5)	0 0.0 (0.0-124.9)	4 0.48 (0.13-1.2)
Other	1 2.2 (0.06-12.4)	0 0.0 (0.0-21.8)	0 0.0 (0.0-49.0)	0 0.0 (0.0-15.1)	0 0.0 (0.0-1.1)	0 0.0 (0.0-6.4)	0 0.0 (0.0-0.92)	0 0.0 (0.0-1.0)	0 0.0 (0.0-124.9)	1 0.12 (0.003-0.66)
Sudden cardiac death	0 0.0 (0.0-8.2)	1 5.9 (0.15-32.9)	0 0.0 (0.0-49.0)	1 4.1 (0.10-22.8)	0 0.0 (0.0-1.1)	0 0.0 (0.0-6.4)	0 0.0 (0.0-0.92)	1 0.27 (0.007-1.5)	0 0.0 (0.0-124.9)	2 0.24 (0.03-0.86)
Unknown	0 0.0 (0.0-8.2)	0 0.0 (0.0-21.8)	0 0.0 (0.0-49.0)	0 0.0 (0.0-15.1)	0 0.0 (0.0-1.1)	0 0.0 (0.0-6.4)	0 0.0 (0.0-0.92)	1 0.27 (0.007-1.5)	3 102.2 (21.1-295.7)	4 0.48 (0.13-1.2)

*Note: * Incidence rate is shown per 10,000 WY*

10.2.6 DNG Long-term use

The VIPOS study followed women with endometriosis up for seven years and provides valuable real-world data on the long-term use of dienogest 2 mg. Previously published data on the safety of dienogest for treatment periods of at least 15 months were derived from studies with relatively low numbers of patients and limited follow-up time (that is, a maximum of 60 months of DNG use) [8].

Long-term use is defined in the VIPOS study as continuous use of the hormonal endometriosis medication for at least 15 months. All intake episodes of a participant were taken into consideration. For example, if a woman used Visanne for 16 months, then stopped and restarted DNG after an intake break of two months, then subsequently used it for additional 20 months before stopping again, two long-term episodes (16 and 20 months) of DNG exposure were taken into consideration for that woman.

A total of 798 women were using DNG 2 mg continuously for 15 months or longer for at least one episode. There were 51 patients with more than one DNG long-term episode (50 women with two episodes and one woman with three long-term episodes) contributing to a total of 850 long-term episodes.

Out of these 798 women, 547 started with DNG 2 mg at study entry and used it continuously for 15 months or longer. A total of 92 women started with Visanne at study entry but took an intake break (either stopping or switching to another EMT), then switched back to Visanne and

subsequently used it for 15 months or longer. A total of 159 women were enrolled with another EMT (85 with GnRH- a, one with Danazol, 51 with CHC and 22 with another progestin) and switched during the follow-up period to Visanne, which they used for at least 15 months.

Table 23 shows the duration of use by time interval. For women with more than one long-term episode, the episode of longest duration was used for this overview. This also applies to the mean duration of DNG use (that is 32.5 months).

Table 23: Duration of DNG use in months: Numbers and percentages of long-term users

Duration of use	DNG long-term user *	
	N	%
15 months	72	9.0
16 to <24 months	237	29.7
24 to <30 months	150	18.8
30 to <36 months	72	9.0
36 to <42 months	66	8.3
42 to <48 months	34	4.3
48 to <54 months	72	9.0
54 to <60 months	26	3.3
60 to <66 months	20	2.5
66 to <72 months	16	2.0
72 to <78 months	23	2.9
78 to <84 months	6	0.8
84 months and more	4	0.5
Total	**798**	100.0

*Note: * Long term use is defined as continuous use of DNG for at least 15 months*

*Note: ** Discrepancy due to rounding*

All participating countries contributed to the data on long-term DNG use as shown in Table 24 (with the majority originating from Hungary).

Table 24: Distribution of long-term DNG users by country: Numbers and percentages

Country	DNG long-term user *	
	N	%
Germany	155	19.4
Poland	40	5.0
Russia	170	21.3
Hungary	369	46.2
Switzerland	15	1.9
Ukraine	49	6.1
Total	**798**	100.0**

*Note: * Long term use is defined as continuous use of DNG for at least 15 months*

*Note: ** Discrepancy due to rounding*

With regard to baseline characteristics of study participants, the only substantial difference between DNG long-term users and the complete DNG cohort was in relation to the classification of an endometriosis diagnosis. Long-term users were more likely to have a surgically confirmed diagnosis of endometriosis (67%) than the complete DNG cohort (47%). There were no considerable differences between the long-term DNG users and the complete DNG cohort in terms of age, BMI, endometriosis-related symptoms or endometriosis-related pain (Table 25).

Table 25: Selected baseline characteristics of all DNG users and DNG long-term users

	DNG long-term* users	All DNG users
Number (%) of women	798 (100%)	3,023 (100%)
Age (years)		
Mean (SD)	35.3 (7.44)	35.1 (7.70)
Age category		
< 20 years	4 (0.5%)	48 (1.6%)
20 to < 30 years	194 (24.3%)	764 (25.3%)
30 to < 40 years	378 (47.4%)	1,399 (46.3%)
>= 40 years	222 (27.8%)	812 (26.9%)
BMI (kg/m^2)		
Mean (SD)	23.6 (4.7)	23.5 (4.4
Diagnosis based on clinical symptoms	265 (33.2%)	1,608 (53.2%)
Diagnosis confirmed by surgery	533 (66.8%)	1,415 (46.8%)
Endometriosis-associated symptoms		
Pelvic pain unrelated to period pain	411 (51.5%)	1,558 (51.5%)
Pain during or after sexual intercourse	291 (36.5%)	1,164 (38.5%)
Painful periods	554 (69.4%)	2,034 (67.3%)
	46 (5.8%)	137 (4.5%)
Endometriosis-related pain - Pain score		
0-3 (mild)	269 (33.7%)	849 (28.1%)
4-7 (severe)	324 (40.6%)	1,462 (48.4%)
8-10 (moderate)	159 (19.9%)	575 (19.0%)

*Note: * Long term use is defined as continuous use of DNG for at least 15 months*

The VIPOS study was not designed to provide details on the efficacy of DNG long-term treatment for endometriosis. The patients were asked at baseline to describe their endometriosis-related symptoms and endometriosis-related pain but were not asked again in the follow-up questionnaire. Consequently, no analysis regarding pain relief or improvement of symptoms during or after DNG long-term treatment was possible.

The safety of DNG long-term use can be assessed by comparing serious adverse events occurring at least 15 months after the start of DNG treatment with those SAEs occurring within the first 14 months of DNG use. Table 26 shows the incidence rates of serious adverse events by organ

system for DNG long-term versus DNG short-term use based on ICD10 coding. The exposure time (in woman years) for DNG long-term use was calculated by summing all intake episodes of 15 months or more of continuous DNG use. The sum of all intake episodes of 14 months or less of DNG intake produced the number of woman years for DNG short-term use.

Table 26: Incidence rate of serious adverse events by organ system for DNG long- and short-term use (according to ICD10)

	DNG Long-term use*	DNG Short-term use**	Total
Number of women-years*	1,360	3,122	4,482
Serious adverse events	50	130	180
IR* *(95% CI)*	367.7 (274.1-481.9)	416.4 (349.1-492.5)	401.6 (346.0-463.3)
Thereof			
Infectious diseases	1 7.4 (0.19-40.9)	4 12.8 (3.5-32.8)	5 11.2 (3.6-26.0)
Neoplasms, malignant	4 29.4 (8.0-75.1)	3 9.6 (2.0-28.1)	7 15.6 (6.3-32.2)
Neoplasms, benign	2 14.7 (1.8-53.0)	3 9.6 (2.0-28.1)	5 11.2 (3.6-26.0)
Blood and blood-forming organs	0 0.0 (0.0-27.1)	0 0.0 (0.0-11.8)	0 0.0 (0.0-8.2)
Endocrine diseases	0 0.0 (0.0-27.1)	1 3.2 (0.08-17.8)	1 2.2 (0.06-12.4)
Mental and behavioral disorders	2 14.7 (1.8-53.0)	6 19.2 (7.1-41.8)	8 17.9 (7.7-35.1)
Diseases of the nervous system	3 22.1 (4.6-64.3)	5 16.0 (5.2-37.3)	8 17.9 (7.7-35.1)
Eye	0 0.0 (0.0-27.1)	0 0.0 (0.0-11.8)	0 0.0 (0.0-8.2)
Ear	0 0.0 (0.0-27.1)	0 0.0 (0.0-11.8)	0 0.0 (0.0-8.2)
Cardiovascular system	8 58.8 (25.4-115.6)	5 16.0 (5.2-37.3)	13 29.0 (15.5-49.6)
Respiratory system	2 14.7 (1.8-53.0)	9 28.8 (13.2-54.7)	11 24.5 (12.3-43.9)
Digestive system	12 88.2 (45.7-153.6)	20 64.1 (39.2-98.8)	32 71.4 (48.9-100.6)
Skin	1 7.4 (0.19-40.9)	1 3.2 (0.08-17.8)	2 4.5 (0.54-16.1)
Musculoskeletal system and connective tissue	4 29.4 (8.0-75.1)	6 19.2 (7.1-41.8)	10 22.3 (10.7-41.0)
Genitourinary system	7 51.5 (20.7-105.8)	49 157.0 (116.3-207.0)	56 125.0 (94.5-162.0)
Pregnancy, delivery, and puerperium	0 0.0 (0.0-27.1)	7 22.4 (9.0-46.1)	7 15.6 (6.3-32.2)
Malformations, deformations and chromosomal abnormalities	0 0.0 (0.0-27.1)	0 0.0 (0.0-11.8)	0 0.0 (0.0-8.2)
Injury, poisoning, accidents, etc.	4 29.4 (8.0-75.1)	11 35.2 (17.6-63.0)	15 33.5 (18.7-55.1)

Note: ***Incidence rate is shown per 10^4 women-years. SAEs, which occurred within 3 months after the stop of EMT, were attributed to the last EMT used by the women. Therefore, pregnancy-related SAEs do not necessarily reflect unwanted pregnancies during EMT use.

A total of 180 SAEs was reported by 157 women, 41 of them reported an SAE after 14 months of DNG use, 122 within the first 14 months of use; six out of these 157 women reported an SAE within the short-term as well as within the long-term intake episode.

The overall SAE incidence rate per 10,000 WY for DNG long-term use was lower compared to DNG short-term use (367.7 and 416.4, respectively). Most of the 180 SAEs were unplanned hospital admissions (due to a variety of reasons). The seven malignant neoplasms reported by DNG users were newly diagnosed after study enrollment (four during DNG long-term and three during DNG short-term use episodes).

Table 44 specifies the ICD10 codes for the SAEs sub- grouped by organ systems in Table 26.

SAEs of the cardiovascular system were more frequently reported after 14 months of DNG intake. Among the eight cases were two DVT (cf. Annex 2.3, VTE case description, case 05067 and 02318) and six unplanned hospital admissions due to other cardiovascular problems. The five cases reported during the first 14 months of DNG use include a DVT and a pulmonary embolism and three cases of unplanned hospitalization due to other cardiovascular problems.

Most of the reported SAEs were associated with the genitourinary system. Among these were 14 unplanned hospitalizations due to ovarian cysts (two during long-term and 12 during short-term DNG use).

As explained in Section 9.4, only women who stopped their treatment for at least three months were assigned to the “Ex-use” cohort. Therefore, the pregnancy-related SAEs were events occurring within three months after the stop of DNG intake.

With regard to the primary outcome of anemia, there was only one confirmed case (according to the study definition) reported by a DNG long-term user (cf. Annex 2.1, DNG case 06491). This event (anemia treated by a physician with iron tablets) was not classified as SAE.

With regard to the other primary outcome of depression, three confirmed cases (according to the study definition) occurred during DNG long-term use (cf. Annex 2.2, DNG - case 03231, 03527, 11913). Case 03527 was classified as SAE because deterioration of her depression led to her unplanned hospitalization.

During the study period, women frequently stopped or switched their endometriosis treatment (including DNG). Table 27 illustrates the DNG use pattern. A total of 3,262 women started DNG use either at study entry or during the subsequent follow-up period.

Most of these DNG users (81.5%) had only one intake episode with a mean duration of 12.2 months of use. However, 602 women had more than one intake episode. Of these 602 women, 467 had two intake episodes, 98 had three intake episodes and 28 had more than three intake episodes. The mean cumulative duration of DNG use for women with two intake episodes was 22.3 months during a mean duration of study participation of 56.4 months. Women with three intake episodes used DNG on average for a total of 28.3 months during a mean duration of study participation of 62.6 months.

Table 27: Pattern of DNG use

Number of DNG intake episodes	No. of women	Duration of DNG episodes in months				Cumulative duration of DNG intake per women in months		Duration of study participation in months	
	N	Mean	Std	Min	Max	Mean	Std	Mean	Std
One episode	2,660	12.2	14.42	1	95	12.2	14.42	45.5	25.17
Two episodes	476	11.1	8.71	1	77	22.3	17.43	56.4	20.39
Three episodes	98	9.4	4.96	1	41	28.3	14.87	62.6	15.20
Four episodes	19	7.1	2.73	1	28	28.3	10.91	63.7	12.56
Five episodes	8	6.6	2.48	1	22	33.1	12.38	69.1	12.43
Six episodes	1	4.8	N/A	2	9	29.0	N/A	57.0	N/A
Total	3,262	11.9	13.49	1	95	14.3	15.57	47.8	24.68

10.3 Main results

10.3.1 Anemia

A total of 197 anemia cases were observed, with an overall incidence rate of 23.4 per 10,000 WY (95% CI, 20.2 – 26.9) as shown in Table 42. The incidence rate (IR) for DNG (33.5 per 10,000 WY; 95% CI, 18.7– 55.1) was lower compared to OAED (49.1 per 10,000 WY; 95%, CI, 25.4 – 85.6). This was similar to the IR of Other progestins (31.3 per 10,000 WY; 95% CI, 18.6 – 49.4), but higher than the IR of all NAED (22.9 per 10,000 WY; 95% CI, 18.5 – 28.1). However, with regard to the more severe cases of anemia (that is, those treated with infusions/injections or blood transfusions), DNG had a lower incidence than OAED and a similar incidence to NAED. Specifically, the incidence of anemia treated with iron infusions/injections was 4.5 per 10,000 WY (95% CI, 0.5 – 16.1), 8.2 per 10,000 WY (95% CI, 1.0 – 29.5) and 3.5 per 10,000 WY (95% CI, 1.9 – 5.9) for DNG, OAED and NAED, respectively. The incidence of anemia treated with blood transfusions was 0.0 per 10,000 WY (95% CI, 0.0 – 8.2), 8.2 per 10,000 WY (95% CI, 1.0 – 29.5) and 0.5 per 10,000 WY (95% CI, 0.1 – 1.8) for DNG, OAED and NAED, respectively.

Incidence rates varied substantially across countries, not only with regard to the confirmed but also with regard to the self-reported cases (cf. Table 62-Table 67). The incidence rates for confirmed cases were considerably higher in Poland, Russia and Hungary compared to Germany or Hungary. In Germany, 10 cases of newly diagnosed anemia were observed, producing an incidence rate of 18.2/10,000 WY, in Poland 17 cases (IR = 43.5/10,000 WY), in Hungary 20 cases (IR = 6.1/10,000 WY), in Russia 120 cases (IR = 35.5/10,000 WY) and in Ukraine 29 cases (IR = 34.7/10,000 WY). The results in relation to Switzerland must be interpreted with caution given the low number of women-years in that country. Absolute numbers and incidence rates of newly diagnosed anemia or reoccurrence of anemia by country are presented in Table 28.

Despite the large variance in country-specific anemia incidence rates, similar trends across countries can be identified in the anemia treatment provided to study participants. Overall, approximately 80% of cases were treated with iron tablets, with the remaining 20% managed with

iron infusion/injections. Anemia requiring a blood transfusion was a rare outcome with an overall incidence rate of 0.7 per 10,000 WY.

Table 28: Newly diagnosed anemia and treatment: Number of cases and incidence rates by country

	Germany	Poland	Hungary	Switzerland	Russia	Ukraine	Total
Number of women-years	5,498	3,908	32,550	84	33,782	8,365	84,187
Anemia							
N *IR ** *(95% CI)*	**10** **18.2** **(8.7-33.4)**	**17** **43.5** **(25.4-69.6)**	**20** **6.1** **(3.8-9.5)**	**1** **119.0** **(3.0-645.5)**	**120** **35.5** **(29.5-42.5)**	**29** **34.7** **(23.2-49.8)**	**197** **23.4** **(20.2-26.9)**
Thereof							
Treated with iron tablets	7 12.7 (5.1-26.2)	13 33.3 (17.7-56.8)	14 4.3 (2.4-7.2)	0 0.0 (0.0-429.6)	104 30.8 (25.2-37.3)	23 27.5 (17.4-41.2)	161 19.1 (16.3-22.3)
Treated with iron infusion/injections	3 5.5 (1.1-15.9)	3 7.7 (1.6-22.4)	5 1.5 (0.50-3.6)	1 119.0 (3.0-645.5)	13 3.8 (2.0-6.6)	5 6.0 (1.9-13.9)	30 3.6 (2.4-5.1)
Treated with blood transfusions	0 0.0 (0.0-6.7)	1 2.6 (0.1-14.3)	1 0.31 (0.0-1.7)	0 0.0 (0.0-429.6)	3 0.9 (0.2-2.6)	1 1.2 (0.0-6.7)	6 0.7 (0.3-1.6)

*Note: * Incidence rate is shown per 10,000 WY*

A Cox regression analysis of anemia cases was carried out in accordance with the final statistical analysis plan. Due to heterogeneity between the country-specific anemia incidence rates, a stratified Cox model was applied. For exploratory purposes only, an analysis not considering country as stratum was carried out as shown in Table 30 The following pre-defined prognostic factors were included in the Cox regression model: age, history of bleeding disorders and history of treated anemia.

Stratified analysis of anemia showed a crude hazard ratio (HR_{crude}) of 1.0 (95% CI, 0.4 – 2.5) for DNG vs. OAED and an adjusted hazard ratio (HR_{adj}) of 1.1 (95% CI, 0.4 - 2.6) (cf. Table 29). The HR_{crude} for DNG vs. OAED in the unstratified analysis was 0.9 (95% CI, 0.4 - 2.0) and HR_{adj} was 1.0 (95% CI, 0.5 - 2.3) (cf. Table 30).

A comparison of the DNG cohort versus NAED showed a slightly elevated risk estimate for DNG, however, results were not statistically significant. An HR_{crude} of 1.4 (95% CI, 0.8 2.4) was observed for anemia in the stratified analysis. The HR_{adj} was 1.3 (95% CI, 0.7 to 2.4). Without stratification by country, the HR_{crude} for DNG vs. NAED was 1.4 (95% CI, 0.8 - 2.4). and HR_{adj} was 1.3 (95% CI, 0.7 - 2.2) (cf. Table 29 and Table 30).

The hazard ratios for DNG versus Ex-use showed a trend toward decreased risk of anemia with DNG. Stratified by country, the observed HR_{crude} was 0.8 (95% CI, 0.3 - 1.9) and the HR_{adj} was 0.7 (95% CI, 0.3 - 1.8). The unstratified, HR_{crude} was 0.7 (95% CI, 0.3 - 1.6) and the HR_{adj} was 0.7 (95% CI, 0.3 - 1.6) (cf. Table 29 and Table 30).

Table 29: New anemia: Number of events, women-years and incidence rates (crude and adjusted) obtained from the Cox model (stratified by country)

Cohorts	No. of events	WY	Incidence rate per 10^4 WY	Crude HR (95 % CI)	Adjusted* HR (95 % CI)
DNG	15	4,482	33.5	1.0	1.1
OAED	12	2,444	49.1	(0.4 - 2.5)	(0.4 - 2.6)
DNG	15	4,482	33.5	1.4	1.3
NAED	92	40,090	22.9	(0.8 - 2.4)	(0.7 - 2.4)
DNG	15	4,482	33.5	0.8	0.7
Ex-use	78	36,877	21.2	(0.3 - 1.9)	(0.3 - 1.8)

*Note: *Adjusted for age, history of bleeding disorders and history of treated anemia.*

Table 30: New anemia: Number of events, women-years, incidence rates and hazard ratios (crude and adjusted) (not stratified)

Cohorts	No. of events	WY	Incidence rate per 10^4 WY	Crude HR (95 % CI)	Adjusted* HR (95 % CI)
DNG	15	4,482	33.5	0.9	1.0
OAED	12	2,444	49.1	(0.4 - 2.0)	(0.5 - 2.3)
DNG	15	4,482	33.5	1.4	1.3
NAED	92	40,090	22.9	(0.8 - 2.4)	(0.7 - 2.2)
DNG	15	4,482	33.5	0.7	0.7
Ex-use	78	36,877	21.2	(0.3 - 1.6)	(0.3 - 1.6)

*Note: *Adjusted for age, history of bleeding disorders and history of treated anemia.*

10.3.2 Depression

A total of 139 cases of depression were observed, with an overall incidence rate of 16.5 per 10,000 WY (95% CI, 13.9-19.5) as shown in Table 43. The incidence rate for the 16 DNG cases (35.7 per 10,000 WY, 95% CI, 20.4-57.9) was considerably higher compared to OAED (2 cases, IR 8.2 per 10,000 WY, 95%CI, 0.99-29.5) or to all NAED (68 cases, IR 17.0 per 10,000 WY, 95%CI 13.2-21.5).
DNG users also had a higher incidence rate of a personal history of depression (6.7/10,000 WY, 95%CI, 1.4-19.5) compared to OAED (4.1/10,000 WY, 95%CI, 0.1-22.8) or to all NAED (3.2/10,000 WY, 95%CI, 1.7-5.5).
The majority of the cases required treatment by a psychiatrist (109 cases, IR 12.9/10,000 WY, 95% CI, 10.6-15.6), 22 cases required hospital admission (IR 2.6/10,000 WY, 95% CI, 1.6-4.0) and 8 cases were associated with a suicide attempt (IR 0.95/10,000 WY, 95% CI, 0.4-1.9). There were no completed suicides in the study. The incidence rate for DNG was higher in all categories of depression cases compared to OAED or NAED.

Similar to the variation in the incidence of anemia between countries, there were also substantial differences between countries in relation to the incidence rate of depression. The highest incidence

rate was observed in Germany (61.8/10,000 WY) and, the lowest in Ukraine (2.4/10,000 WY) as shown in Table 31. There were no confirmed cases of depression in Switzerland[17].

When taking into consideration all self-reported cases of depression (that is, not restricting the analysis to confirmed cases), the marked differences between the countries were already present (cf. Table 68 - Table 73). The incidence rate of self-reported depression cases in Germany was 687.6/10,000 WY (95%CI, 622.1-757.7) compared to Russia with 49.1/10,000 WY (95% CI, 42.0-57.2) or Hungary (IR 79.9/10,000 WY, 95% CI,70.5-90.2). This variation reflects not only differences in the diagnosis of depression within the context of the different health care systems but also most likely cultural differences which influence the reporting of depression.

Table 31: New depression or worsening of existing depression: Number of events, women-years and incidence rates by country

Depression	Germany	Poland	Hungary	Switzerland	Russia	Ukraine	Total
Number of women-years	5,498	3,908	32,550	84	33,782	8,365	84,187
Depression							
N *IR ** *(95% CI)*	**34** **61.8** **(42.9-86.3)**	**12** **30.7** **(15.9-53.6)**	**70** **21.5** **(16.8-27.2)**	**0** **0.0** **(0.0-429.6)**	**21** **6.2** **(3.8-9.5)**	**2** **2.4** **(0.3-8.6)**	**139** **16.5** **(13.9-19.5)**
Thereof							
Treated by psychiatrist	21 38.2 (23.7-58.3)	12 30.7 (15.9-53.6)	60 18.4 (14.1-23.7)	0 0.0 (0.0-429.6)	16 4.7 (2.7-7.7)	0 0.0 (0.0-4.4)	109 12.9 (10.6-15.6)
Hospital admission	11 20.0 (10.0-35.8)	0 0.0 (0.0-9.4)	6 1.8 (0.7-4.0)	0 0.0 (0.0-429.6)	4 1.2 (0.3-3.0)	1 1.2 (0.0-6.7)	22 2.6 (1.6-4.0)
Suicide attempt	2 3.6 (0.4-13.1)	0 0.0 (0.0-9.4)	4 1.2 (0.3-3.1)	0 0.0 (0.0-429.6)	1 0.30 (0.0-1.6)	1 1.2 (0.0-6.7)	8 0.95 (0.4-1.9)
Committed suicide	0 0.0 (0.0-6.7)	0 0.0 (0.0-9.4)	0 0.0 (0.0-1.1)	0 0.0 (0.0-429.6)	0 0.0 (0.0-1.1)	0 0.0 (0.0-4.4)	0 0.0 (0.0-0.4)
Personal history of depression	10 18.2 (8.7-33.4)	2 5.1 (0.6-18.5)	11 3.4 (1.7-6.0)	0 0.0 (0.0-429.6)	1 0.30 (0.0-1.6)	0 0.0 (0.0-4.4)	24 2.9 (1.8-4.2)
Family history of depression	10 18.2 (8.7-33.4)	2 5.1 (0.6-18.5)	9 2.8 (1.3-5.2)	0 0.0 (0.0-429.6)	3 0.89 (0.2-2.6)	0 0.0 (0.0-4.4)	24 2.9 (1.8-4.2)

*Note: * Incidence rate per 10,000 WY*

A Cox proportional hazard model was applied in accordance with the final statistical analysis plan. Country was included as stratum to account for heterogeneity. Analysis without stratification by country was carried out for exploratory reasons only and is shown below in Table 33.

[17] It was not possible to obtain medical confirmation for depression cases in Switzerland. Four cases remained therefore potential cases.

The following prognostic factors were included in the Cox regression model: age, family and personal history of depression at baseline and use of antidepressants (at baseline and during follow-up).

When stratified by endometriosis treatment (sub-)cohort, there were 16 cases in the DNG cohort, 2 cases in the OAED cohort, 68 cases in the NAED cohort and 53 cases in the Ex-use cohort (cf. Table 32 and Table 33).

In the final analysis, model stratified by country (cf. Table 32) the crude hazard ratio (HR_{crude}) for DNG vs. OAED was 1.9 (95% CI, 0.4 - 9.7). The adjusted hazard ratio (HR_{adj}) was 1.8 (95% CI, 0.3 - 9.4). There were only two depression cases in the OAED cohort, and the confidence interval is therefore relatively wide. The HR_{crude} for DNG vs. NAED and DNG vs. Ex-use was 1.6 (95% CI, 0.9-2.8) and 1.2 (95% CI, 0.6-2.5), respectively. The comparisons of DNG vs. NAED and DNG vs. Ex-use resulted in an HR_{adj} of 1.5 (95% CI, 0.8-2.8) and 1.2 (95% CI, 0.6-2.5). Although per protocol, the results did not allow for a two-fold risk for depression to be excluded, the adjusted hazard ratio of 1.5 with an upper 95% confidence limit of 2.8 suggests that it was very unlikely that the relative risk of DNG vs. NAED exceeds three.

Table 32: New depression or deterioration of existing depression: Number of events, women-years, incidence rates and hazard ratios (crude and adjusted) obtained from the Cox model stratified by country

Cohorts	No. of events	WY	Incidence rate per 10^4 WY	Crude HR (95 % CI)	Adjusted* HR (95 % CI)
DNG	16	4,482	35.7	1.9	1.8
OAED	2	2,444	8.2	(0.4 - 9.7)	(0.3 - 9.4)
DNG	16	4,482	35.7	1.6	1.5
NAED	68	40,090	17.0	(0.9 - 2.8)	(0.8 - 2.8)
DNG	16	4,482	35.7	1.2	1.2
Ex-use	53	36,877	14.4	(0.6 - 2.5)	(0.6 - 2.5)

*Note: *Adjusted for age, family and personal history of depression at baseline and use of antidepressants (at baseline and during follow-up).*

In the unstratified analysis, the HR_{crude} for DNG vs. OAED was 5.0 (95% CI, 1.1 - 22.3) and the HR_{adj} was 3.4 (95% CI, 0.8 - 15.7). A comparison of the DNG cohort versus NAED showed a HR_{crude} of 2.1 (95% CI, 1.2 - 3.6) and a HR_{adj} of 2.0 (95% CI, 1.1 - 3.6). The hazard ratios for DNG versus Ex-use showed a HR_{crude} of 1.8 (95% CI, 0.9 - 3.6) and the HR_{adj} was 1.6 (95% CI, 0.8 - 3.4) (cf. Table 33).

Table 33: New depression or deterioration of existing depression: Number of events, women-years, incidence rates and hazard ratios (crude and adjusted) from the Cox model, not stratified

Cohorts	No. of events	WY	Incidence rate per 10^4 WY	Crude HR (95 % CI)	Adjusted* HR (95 % CI)
DNG	16	4,482	35.7	5.0	3.4
OAED	2	2,444	8.2	(1.1 - 22.3)	(0.8 - 15.7)
DNG	16	4,482	35.7	2.1	2.0
NAED	68	40,090	17.0	(1.2 - 3.6)	(1.1 - 3.6)
DNG	16	4,482	35.7	1.8	1.6
Ex-use	53	36,877	14.4	(0.9 - 3.6)	(0.8 - 3.4)

*Note: *Adjusted for age, family and personal history of depression at baseline and use of antidepressants (at baseline and during follow-up).*

The Safety Monitoring and Advisory Committee suggested a sensitivity analysis regarding confirmed depression cases without any history of depressive episodes. Therefore, an analysis was conducted which took into consideration only confirmed cases according to the study definition with no history of depression at all (that is, not only without a personal history of treated depression reported at baseline as displayed in table 43, but also without any self-reported depressive episode before the confirmed event occurred and with no previous use of antidepressants). This produced a total of 103 depression cases: 10 in the DNG cohort (IR = 22.3 per 10,000 WY), one in the OAED cohort (IR = 4.1/10,000 WY), 51 in the NAED cohort (IR = 12.7/10,000WY) and 41 in Ex-use (IR = 11.1/10,000 WY) (cf. Table 34).

Stratified Cox regression including the same prognostic factors was conducted and resulted in an adjusted hazard ratio for DNG vs. OAED of 3.1 and a broader 95% confidence interval of 0.3 to 30.8 because only one depression case was observed in the OAED cohort. Comparing DNG vs. NAED the HR_{adj} was 2.1 (95% CI, 1.0 - 4.3) (cf. Table 34).

Table 34: New depression: Number of events, women-years, incidence rates and hazard ratios (crude and adjusted) obtained from the Cox model stratified by country

Cohorts	No. of events	WY	Incidence rate per 10^4 WY	Crude HR (95 % CI)	Adjusted* HR (95 % CI)
DNG	10	4,482	22.3	3.2	3.1
OAED	1	2,444	4.1	(0.3 - 31.1)	(0.3 - 30.8)
DNG	10	4,482	22.3	1.5	2.1
NAED	51	40,090	12.7	(0.8 - 3.1)	(1.0 - 4.3)
DNG	10	4,482	22.3	1.3	1.4
Ex-use	41	36,877	11.1	(0.6 - 2.9)	(0.6 - 3.2)

*Note: *Adjusted for age, family and personal history of depression at baseline and use of antidepressants (at baseline and during follow-up).*

The a priori, per protocol, definition of depression was relatively strict, and the total number of observed cases was lower than assumed. Therefore, the Safety Monitoring and Advisory Committee requested a sensitivity analysis broadening the definition of depression to include all confirmed cases (n=139) plus 'unconfirmed' reported depression cases where the study participant had no previous depressive episodes and no history of antidepressant use at baseline. An additional 80 cases were included in this analysis, for a total number of observed depression cases of 219: 24 DNG cases, nine OAED cases, 101 NAED cases, and 85 Ex-use cases.

Stratified Cox regression analysis using the same prognostic factors revealed an adjusted hazard ratio for DNG vs. OAED of 0.5 (95% CI, 0.2 - 1.3). The HR_{adj} for DNG vs. NAED was 1.3 (95% CI, 0.8 - 2.2) and for DNG vs Ex-use it was 1.2 (95% CI, 0.7 - 2.2) (cf. Table 35).

Table 35: Confirmed depression and potential depression without a history of depressive episodes: Number of events, women-years, incidence rates and hazard ratios (crude and adjusted) obtained from the Cox model stratified by country

Cohorts	No. of events	WY	Incidence rate per 10^4 WY	Crude HR (95 % CI)	Adjusted* HR (95 % CI)
DNG	24	4,482	53.6	0.5	0.5
OAED	9	2,444	36.8	(0.2 - 1.3)	(0.2 - 1.3)
DNG	24	4,482	53.6	1.3	1.3
NAED	101	40,090	25.2	(0.8 - 2.1)	(0.8 - 2.2)
DNG	24	4,482	53.6	1.1	1.2
Ex-use	85	36,877	23.0	(0.6 - 2.0)	(0.7 - 2.2)

*Note: *Adjusted for age, family and personal history of depression at baseline and use of antidepressants (at baseline and during follow-up).*

An additional sensitivity analysis was conducted which combined all confirmed cases (n = 139) and cases treated with antidepressants by a general practitioner. This increased the total number of cases to 151; there were five additional cases in the DNG and NAED cohorts and two additional cases in Ex-use. The number of depression cases in the OAED cohort did not change (n = 2) (that is, it remained low). Therefore, the confidence intervals for DNG vs. OAED were wide compared with NAED and Ex-use. Stratified Cox regression analysis was conducted. The adjusted hazard ratio for DNG vs. OAED was 2.6 (95% CI, 0.5 - 13.2) and the HR_{adj} for DNG vs. NAED and DNG vs. Ex-use were 1.8 (95% CI, 1.0 - 3.2) and 1.5 (95% CI, 0.8 - 2.9), respectively (cf. Table 36).

Table 36: Confirmed depression and depression treated with antidepressants by general practitioners: Number of events, women-years, incidence rates and hazard ratios (crude and adjusted) obtained from the Cox model stratified by country

Cohorts	No. of events	WY	Incidence rate per 10^4 WY	Crude HR (95 % CI)	Adjusted* HR (95 % CI)
DNG	21	4,482	46.9	2.7	2.6
OAED	2	2,444	8.2	(0.5 - 13.6)	(0.5 - 13.2)
DNG	21	4,482	46.9	1.8	1.8
NAED	73	40,090	18.2	(1.1 - 3.0)	(1.0 - 3.2)
DNG	21	4,482	46.9	1.5	1.5
Ex-use	55	36,877	14.9	(0.8 - 2.8)	(0.8 - 2.9)

*Note: *Adjusted for age, family and personal history of depression at baseline and use of antidepressants (at baseline and during follow-up).*

In addition, the Safety Monitoring and Advisory Committee was interested in the specific risks associated with age and requested additional analysis stratifying the study population by age. Therefore, stratified Cox proportional hazard models were conducted separately for women younger than 25 years of age and 25 years and older at study entry. The cut-off of 25 years was chosen based on the current understanding of the adolescent brain and brain maturation nine. Cases were allocated to groups based on the study participant's age at baseline. We assumed; a) that time to a depression diagnosis following a 'trigger' event is variable and b) if endometriosis treatment interacts differently in the adolescent brain, capturing study participants exposed whilst <25 years was important for stratification.

A total of 40 cases of depression were observed in women younger than 25 years: DNG four cases, OAED no cases, NAED 26 cases, and Ex-use 10 cases. The total number of WY of observation attributed to this cohort was 20,881 WY, with the majority contributed by the NAED and Ex-use cohorts. The depression incidence rates for women under 25 years were 106.3 per 10,000 WY for the DNG cohort and 0.0, 21.0 and 12.5 for the OAED, NAED and Ex-use cohorts, respectively. Stratified Cox regression analysis was applied only for DNG vs. NAED and DNG vs. Ex-use, due to the missing number of events in the OAED cohort. This analysis resulted in HR_{adj} of 4.4 (95% CI, 1.3 - 14.5) for DNG vs. NAED and 7.5 (95% CI, 1.8 - 31.8) for DNG vs. Ex-use (cf. Table 37).

Table 37: Confirmed depression for women < 25 years at study entry: Number of events, women-years, incidence rates and hazard ratios (crude and adjusted) obtained from the Cox model stratified by country

Cohorts	No. of events	WY	Incidence rate per 10^4 WY	Crude HR (95 % CI)	Adjusted* HR (95 % CI)
DNG	4	376	106.3	NA	NA
OAED	0	133	0.0		
DNG	4	376	106.3	4.7	4.4
NAED	26	12,365	21.0	(1.4 - 15.1)	(1.3 - 14.5)
DNG	4	376	106.3	9.2	7.5
Ex-use	10	8,007	12.5	(2.3 - 36.8)	(1.8 - 31.8)

*Note: *Adjusted for age, family and personal history of depression at baseline and use of antidepressants (at baseline and during follow-up).*

For women 25 years and older at study entry, 12 cases were observed in the DNG cohort (IR = 29.2/10,000 WY), two cases in the OAED cohort (IR = 8.7/10,000 WY), 42 cases in the NAED cohort (IR = 15.1/10,000 WY) and 43 cases in the Ex-use cohort (IR = 14.9/10,000 WY). Stratified Cox regression with the same prognostic factors resulted in an adjusted hazard ratio for DNG vs. OAED of 1.8 (95% CI, 0.3 - 9.6) and 1.1 (95% CI, 0.5 - 2.2) for DNG vs. NAED, respectively. Robust conclusions on differences between the cohorts cannot be derived from the analysis of DNG vs. OAED. Overall, the small numbers and wide confidence interval do not provide sufficient data for meaningful conclusions to be made (cf. Table 38).

Table 38: Confirmed depression for women >=25 years at study entry: Number of events, women-years, incidence rates and hazard ratios (crude and adjusted) obtained from the Cox model stratified by country

Cohorts	No. of events	WY	Incidence rate per 10^4 WY	Crude HR (95 % CI)	Adjusted* HR (95 % CI)
DNG	12	4,106	29.2	1.8	1.8
OAED	2	2,311	8.7	(0.3 - 9.3)	(0.3 - 9.6)
DNG	12	4,106	29.2	1.2	1.1
NAED	42	27,725	15.1	(0.6 - 2.4)	(0.5 - 2.2)
DNG	12	4,106	29.2	0.8	0.8
Ex-use	43	28,870	14.9	(0.4 - 1.8)	(0.3 - 1.8)

*Note: *Adjusted for age, family and personal history of depression at baseline and use of antidepressants (at baseline and during follow-up).*

10.3.3 Treatment discontinuation due to treatment failure

From a total of 42,342 treatment starts, there were 4,733 observed treatment failures with an incidence proportion (IP) of 11.2 per 100 treatment starts. Treatment failure was defined as the cessation of treatment caused by lack of efficacy, loss of efficacy or an adverse drug reaction. The DNG cohort experienced 668 treatment failures from 4,137 starts (IP = 16.1 per 100 starts), the OAED cohort observed 203 treatment failures from 4,001 treatments starts (IP = 5.1 per 100 starts), and the NAED cohort observed 3,862 treatment failures from 34,204 treatment starts (IP = 11.3 per 100 starts) (cf. Table 39).

At the request of the Safety Monitoring and Advisory Committee, treatment failure was divided into two outcomes: medication ineffective and treatment stop due to side effects. In all (sub-)cohorts 'side effects' were reported more frequently than 'medication ineffective' as a reason to stop or switch treatment. DNG users reported that they stopped or switched their treatment due to side effects 558 times (IP =13.5 per 100 starts) and medication ineffective 144 times (IP = 3.5 per 100 starts). OAED users reported side effects as the reason for discontinuation 152 times (IP = 3.8 per 100 starts) and medication effective 59 times (IP = 1.5 per 100 starts). NAED users reported side effects 3,387 times (IP = 9.9 per 100 starts) and medication ineffective 560 times (IR = 1.6 per 100 starts) (cf. Table 39).

Table 39: Treatment discontinuation due to treatment failure by user (sub-)cohort: Number of treatment starts, numbers of reports and incidence proportions

	DNG	OAED			NAED			Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED	
Number of treatment starts	4,137	2,831	1,170	4,001	28,074	5,559	34,204	42,342
Treatment failure								
N *IP ** *(95% CI)*	**668** **16.1** **(15.0-17.3)**	**148** **5.2** **(4.4-6.1)**	**55** **4.7** **(3.6-6.1)**	**203** **5.1** **(4.4-5.8)**	**3,244** **11.6** **(11.2-11.9)**	**554** **10.0** **(9.2-10.8)**	**3,862** **11.3** **(11.0-11.6)**	**4,733** **11.2** **(10.9-11.5)**
*Thereof ***								
Medication ineffective	144 3.5 (2.9-4.1)	40 1.4 (1.0-1.9)	19 1.6 (1.0-2.5)	59 1.5 (1.1-1.9)	406 1.4 (1.3-1.6)	140 2.5 (2.1-3.0)	560 1.6 (1.5-1.8)	763 1.8 (1.7-1.9)
Side effects	558 13.5 (12.5-14.6)	116 4.1 (3.4-4.9)	36 3.1 (2.2-4.2)	152 3.8 (3.2-4.4)	2,895 10.3 (10.0-10.7)	440 7.9 (7.2-8.7)	3,387 9.9 (9.6-10.2)	4,097 9.7 (9.4-10.0)

*Note: * Incidence proportion per 100 treatment starts, including exposure at study entry, switches between exposure groups and/or restarts within exposure groups.*
*Note: ** Multiple responses were possible.*

The OAED (sub-)cohorts of GnRH-a and Danazol typically have a limited duration of use; GnRH-a is normally prescribed for six months and Danazol users are advised not to take the medication on a continuous, long-term basis without an intake break. Therefore, the Safety Monitoring and Advisory Committee requested a separate sensitivity analysis looking specifically at the first six months of treatment for a better comparison between DNG and OAED users.

A total of 2,452 treatment failures from 17,419 treatment starts were observed, resulting in an incidence proportion of IP = 14.1 per 100 starts. The incidence proportions per 100 treatment starts by sub-(cohort) are as follows: DNG: 20.4; OAED: 6.0; NAED: 4.8. When the analysis was restricted to treatment failure due to self-reported side effects, the incidence proportions per 100 treatment starts were: DNG: 17.7; OAED: 4.6 and NAED: 12.9) (cf. Table 40).

Table 40: Discontinuation due to treatment failure in the first 6 months of an EMT intake episode: Number of treatment starts, number of reports and incidence proportions

	DNG	OAED			NAED			Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED	
Number of treatment starts	1,840	1,880	747	2,627	10,184	2,496	12,952	17,419
Treatment failure								
N	**376**	**118**	**40**	**158**	**1536**	**339**	**1918**	**2452**
*IP **	**20.4**	**6.3**	**5.4**	**6.0**	**15.1**	**13.6**	**14.8**	**14.1**
(95% CI)	**(18.6-22.4)**	**(5.2-7.5)**	**(3.9-7.2)**	**(5.1-7.0)**	**(14.4-15.8)**	**(12.3-15.0)**	**(14.2-15.4)**	**(13.6-14.6)**
*Thereof***								
Medication ineffective	75 4.1 (3.2-5.1)	30 1.6 (1.1-2.3)	11 1.5 (0.7-2.6)	41 1.6 (1.1-2.1)	212 2.1 (1.8-2.4)	89 3.6 (2.9-4.4)	309 2.4 (2.1-2.7)	425 2.4 (2.2-2.7)
Side effects	325 17.7 (15.9-19.5)	93 4.9 (4.0-6.0)	29 3.9 (2.6-5.5)	122 4.6 (3.9-5.5)	1358 13.3 (12.7-14.0)	271 10.9 (9.7-12.1)	1665 12.9 (12.3-13.4)	2112 12.1 (11.6-12.6)

*Note: * Incidence proportion is shown per 100 treatment starts, including exposure at study entry, switches between exposure groups and/or restarts within exposure groups.*
*Note: ** Multiple responses possible.*

Treatment failure data were analyzed in accordance with the final statistical analysis plan. The labeled duration of use varied between the medications used by the (sub-)cohorts and it was, therefore, not considered appropriate to base the treatment failure analysis on time-to-event. Treatment failure may occur at multiple points in time during follow-up if multiple successive treatment episodes are present. Clustering per subject is accounted for within the application of generalized estimating equations (GEE). Crude and adjusted odds ratios were calculated. The following potential confounders were incorporated into the model: age, family and personal history of depression and severity of pain (pain scale between 8-10) at baseline. The results are shown in Table 41.

The crude odds ratio (OR_{crude}) for DNG vs. OAED was 3.7 (95% CI, 3.1 - 4.4). The adjusted odds ratio (OR_{adj}) was 3.4 (95% CI, 2.8 - 4.0). A comparison of DNG vs. NAED showed a lower risk estimate, specifically an OR_{crude} of 1.5 (95% CI, 1.4 - 1.7). The odds ratio did not change when adjusted for the pre-defined potential confounders (OR_{adj} 1.5; 95% CI, 1.4 - 1.7).

Table 41: Risk of treatment discontinuation due to treatment failure: Number of events, number of treatment starts and incidence rates

Cohorts	No. of events	Treatment starts	Incidence rate per 100 starts	Crude OR (95 % CI)	Adjusted* OR (95 % CI)
DNG	668	4,137	16.1	3.7	3.4
OAED	203	4,001	5.1	(3.1 - 4.4)	(2.8 - 4.0)
DNG	668	4,137	16.1	1.5	1.5
NAED	3862	34,204	11.3	(1.4 - 1.7)	(1.4 - 1.7)

*Note: *Adjusted for age, family and personal history of depression and severity of pain (pain scale between 8-10) at baseline*

10.4 Other Analyses

Not applicable.

10.5 Adverse events/adverse reactions

Adverse events/adverse reactions are described in Section 10.2.5.

11. Discussion

11.1 Key results

The VIPOS study, a prospective, non-interventional, active surveillance cohort study, was designed to characterize and compare the short- and long-term risks associated with the use of DNG, OAED and NAED, and in particular, the risk of new and worsening depression, anemia and treatment failure under routine clinical conditions. In the study, clinical outcomes reported in these three (sub-)cohorts were analyzed and compared. It is understood to be the largest real-world non-interventional study of the medical treatment of women with endometriosis and was optimized to capture sensitive patient-reported data and powered to determine the safety of dienogest 2 mg compared with other available hormonal endometriosis treatments.

The difficulties encountered during study conduct regarding the predicted background incidence of depression and anemia and considerable inter-country variance in both endometriosis diagnosis, treatment patterns and incidence of self-reported anemia and depression make interpretation of results challenging. Overall, the data does not support the drawing of robust conclusions to be drawn regarding the primary outcomes of interest.

Never-the-less, the study supports the following conclusions. The following conclusions drawn by the principal investigator were endorsed by the Safety Monitoring and Advisory Committee on January 26, 2019:

Baseline Characteristics

- DNG and OAED users had similar characteristics, whereas NAED users differed on age, severity level of endometriosis and confirmation of diagnosis.
- Baseline data captured provides valuable insight into the patient journey, disease, and its impact, in a real-world setting.
- Widespread use of empirical treatment suggests a general acceptance of clinical symptom diagnosis for endometriosis as supported by international guidelines [10].
- Women with endometriosis often experienced multiple symptoms of the disease, including pain during menstruation and heavy and/or irregular periods.
- Endometriosis-related pain was frequently experienced by women but differed in severity between countries.
- There is considerable inter-country variance in both endometriosis diagnosis and treatment patterns
    - Swiss data should be interpreted with caution due to a lack of sufficient data
    - Hungarian study population on average was younger and reported less severe endometriosis symptoms

Follow-up

- The overall loss to follow-up rate was 16.8%, which was higher compared to other studies using this study methodology.
- Type and frequency of fatal outcome do not indicate a higher risk for DNG users compared to OAED and NAED.
- There is considerable inter-country variance in incidence of self-reported anemia and depression
- The overall incidence rate for confirmed new or worsening depression was markedly lower than anticipated
- A two-fold risk of depression in DNG users compared to OAED or NAED cannot be excluded
- The overall incidence rate of confirmed, clinically relevant anemia was lower than expected
- A two-fold risk of anemia in DNG users compared to OAED and NAED cannot be excluded – however, a threefold risk for this comparison can be excluded
- An association between age under 25 years, DNG and depression was seen, however, the absolute number of depressive events and overall observation time in this sub-cohort were sparse making interpretation of the results difficult.
- VIPOS demonstrates that, across Europe, that those women who initiate dienogest 2 mg are able to continue with long-term treatment for more than 15 months.

Overall, the VIPOS study furthers our understanding of endometriosis management in clinical practice, presenting extensive data on the type of diagnosis and pharmacological treatment patterns in different European countries.

11.2 Limitations

The possibility of bias and residual confounding can never be eliminated in non-experimental studies such as INAS-VIPOS, and the ability to infer causation is correspondingly limited [11]. Valid information on potential sources of confounding and sophisticated statistical and epidemiologic methodology help to reduce the impact of bias and residual confounding [12]. However, the difficulty remains unresolved when all that exists is a weak association [13,14]. Relative risk estimates that are close to unity may not allow differentiation between causation, bias, and confounding [15,16]. In general, a strict causal interpretation of a relative risk of two or less is difficult in observational research [17].

The VIPOS Study benefited from several strengths which minimized the effects of bias and confounding. For example, the health care professionals who recruited patients in the VIPOS Study were representative of health care professionals who treat endometriosis in their respective countries and comprised gynecologists and specialized centers; selection bias was, therefore, unlikely to have had a substantial impact on the findings. Furthermore, HCPs were expected to enroll all patients who were willing to participate and who fulfilled the other eligibility criteria, thereby minimizing enrollment bias.

The results are also unlikely to have been substantially affected by misclassification bias. By utilizing an active surveillance approach, we were able to capture precise information on treatment exposure, patterns of use (for example, stopping, switching, restarting) and outcomes of interest. By continuing to follow-up patients who deviated from their baseline prescription, we contributed with the 'real world' aspect of our study.

A substantial strength of the VIPOS Study was that it benefited from a study design that enabled us to capture information on important potential confounding variables (for example, antidepressant use and history of depression). Inclusion of these variables in the statistical models enriched our understanding and interpretation of the data.

Whilst recall bias is a potential problem in all studies dealing with information from the past, there is no reason to assume a differential effect for the participants in the present study. Since the self-administered standardized questionnaires for all cohorts are identical, the chance of reporting-related or questionnaire-related bias was small, and, most importantly, would also not have been differential for different cohorts. The important information needed in the context of this study, including for example past history of depression or anemia, were asked in a way to ensure relevant information by asking for additional, specific information on confirmatory evidence (for example time of diagnosis, the specialty of diagnosing/treating HCP). The aim was to capture only significant events that needed treatment by a specialist or hospitalization, thereby reducing potential recall bias.

An additional, potentially limiting factor with respect to the evaluation of potential risk differences for depression was the lack of information on social risk factors which could have influenced the occurrence of depression such as significant life changes (unemployment, partnership status, just to name a few). However, here too there was no reason to assume the differential occurrence of such factors in the two main cohorts (DNG, OAED).

The loss-to-follow-up rate in the VIPOS Study was ultimately higher than we had originally anticipated. Our estimates had been based on study populations of contraceptive users. However, the participatory behavior of women with endometriosis differed from that of typical contraceptive users. We witnessed an increasing reluctance to participate in a longer follow periods and to share updated contact details. The latter may in part be due to increasing awareness of data protection issues; the European Union heralded in the General Data Protection Regulation (GDPR) in May 2018. Theoretically, a greater percentage of SAEs (including depression and anemia cases) may have occurred in patients lost to follow-up; women may have neglected to respond (or been prevented from responding) due to poor mental or physical health. It is unknown what effect the inclusion of data from women lost to follow-up may have had on the study results. However, it is reassuring that the impact would likely be shared approximately equally between the user cohorts – the lost-to-follow-up rates were similar in all cohorts.

The following methodological strengths of the VIPOS Study validate the results: (1) prospective, comparative cohort design; (2) availability of important confounder information (for example use of antidepressants, family history of depression); (3) validation of outcomes of interest and the exposure of the relevant cases; (4) comprehensive follow-up procedures; (5) independent, blinded adjudication of anemia and depression cases; (6) relevant statistical analyses (for example, stratified analyses by country and user (sub-)cohort); sensitivity analyses, outcome definition, prognostic factor/covariate selection and choice of comparator cohorts; (7) representative study population; (8) supervision by an independent Safety Monitoring and Advisory Council, and (9) scientific independence from the study funder.

Although there are inherent limitations within the boundaries of observational research, the VIPOS Study benefited from a methodology that optimized the validity and generalizability of its findings.

11.3 Interpretation

Overall, the goal specified in the study objectives – to exclude a twofold risk for clinically relevant anemia and depression, respectively – could not be reached for DNG versus OAED. There were two main reasons:

1. The assumption for the sample size calculation for both outcomes was an incidence of 100 cases per 10,000 WYs.

   Altogether, 948 depressive events were reported by the study participants, resulting in an incidence of 113 cases/10,000 WYs. However, during the validation process using the strict study criteria for depression, only 139 cases were confirmed as study-relevant depressive events: 16.5/10,000 WYs. Due to this unexpectedly low incidence of events, the power of

the study was insufficient to exclude a two-fold risk comparing the risk of newly diagnosed depressions or deterioration of existing depressions of DNG compared OAED.

The overall incidence of self-reported anemia events during the study period was 113.7 per 10,000 WYs. This approximated the predicted incidence of 100/10,000 WYs. However, as with depression, the incidence rate significantly decreased once the *a priori* study diagnostic algorithm was applied and the final incidence rate for anemia was 23.4/10,000 WYs.

2. There was a higher than expected proportion of study observation time attributed to the 'ex-use' (sub-)cohort.

It was assumed that women who stopped hormonal treatment for endometriosis during study conduct would switch to another active treatment, without or without a treatment break. However, a significant proportion of study participants did not recommence hormonal treatment for endometriosis during study conduct, and yet, continued to contribute to overall study observation time. Overall more than 36,000 WYs were observed in the 'ex-use' (sub-) cohort.

Newly diagnosed depression or deterioration of an existing depression

There was significant inter-country variance in both endometriosis treatment and incidence of depression. The risk differences for newly diagnosed depression or worsening of an existing depression were more pronounced than the differences between the different treatment cohorts. This can potentially be explained by differences in diagnostic/treatment schemes for depressive disorders between countries. Therefore, in addition to the prespecified covariates (age, family and personal history of depression at baseline and use of antidepressants (at baseline and during follow-up)) a stratification by country was built into the COX model. The adjusted hazard ratio comparing the depression risk of DNG and OAED was 1.8 (95% CI: 0.3-9.4). There were only two confirmed cases in the OAED cohort, resulting in a very wide confidence interval and interpretation challenging. On sum the results appear unequivocal, however, a slight increase in risk for DNG cannot be excluded.

A sensitivity analysis including 'potential' cases that is cases for which the blinded adjudicators, based on the available information, could not decide whether it was a confirmed or unconfirmed case, found an adjusted HR for DNG versus OAED of 0.5 (95% CI: 0.2 – 1.3), further illustrating the lack of certainty around interpretation of results.

The SMAC also requested a sensitivity analysis that included cases which had been treated only by a GP and, therefore, had not fulfilled the study criterium for a new or worsening depressive episode. This resulted in an adjusted hazard ratio of 2.6 (95% CI: 0.5 – 13.2).

Overall, the range of risk estimates in the different analyses, including the primary analysis and sensitivity analyses, vary between 0.5 and 2.6. This underlines the instability of the findings. However, based on these results a slightly increased risk for first time occurrence of clinically

relevant depression or worsening of existing depressions of DNG compared to OAED cannot be excluded.

Medical intervention for clinically symptomatic Anemia

As with depression, the pronounced country differences observed with anemia diagnoses meant that country was included in all statistical regression models.

The adjusted hazard for new or reoccurring clinically relevant anemia comparing DNG and OAED was 1.1 (95% CI: 0.4 – 2.6) - a threefold risk could be excluded.

Discontinuation pattern of DNG and other endometriosis treatments due to treatment failure

The proportion of DNG reporting "side effects" or "medication ineffective" as reasons for stopping the treatment was higher compared to OAED users and was more comparable to NAED users. OAED users may be more tolerable towards side effects as they knew at treatment start already that the medication they were taking had a more restrictive treatment duration and a method of administration which did not allow immediate discontinuation and that discontinuation could not be controlled by the patient (for example injectable 3-month depot).

There were substantial differences between countries. The highest proportion[18] of women who reported a treatment failure were found in Germany – however, there was no difference between DNG (33.7%) and OAED users (30.4%). Substantial differences between these two cohorts could only be seen and Hungary (20.8% DNG & 5.6 OAED%) and in Poland (23.7% DNG & 15.5% OAED). In Russia (6.6% DNG & 4.4% OAED) and Ukraine (5.3% DNG & 3.0% OAED), these proportions and the differences between cohorts were markedly smaller. In sum, there is no clear picture across countries regarding treatment failure as the reason for stopping the medication differing between the two main cohorts.

Overall, it is difficult to interpret these results owing to the heterogeneity of the 'treatment failure' grouping and the differences in indicated duration of treatment for DNG, GnRH-a, and Danazol.

DNG long-term use

In total, 798 women in the VIPOS study used DNG continuously for at least 15 months. The mean duration of use was 32.5 months.

The overall SAE incidence rate per 10,000 WY for DNG long-term use was lower compared to DNG short-term use (367.7, 95%CI: 274.1-484.8 and 416.4, 95% CI: 349.1-492.5 respectively).

[18] Incidence proportion per 100 treatment starts (%)

11.4 Generalizability

The study was designed to reflect routine clinical use of hormonal medications as treatment for endometriosis. All new users of a hormonal endometriosis treatment could participate in this study. Study participants were recruited via a large multinational network of 1,027 prescribers. Participation was not limited by medical inclusion and exclusion criteria. We observed a large inter-country variance in endometriosis treatment patterns and the severity of endometriosis diagnosed rendering comparisons across countries and (sub-)cohorts difficult. These differences were not foreseen during study development, largely owing to a dearth of published data on endometriosis diagnosis, management, and drug utilization patterns. Therefore, the study results of this study cannot necessarily be generalized to other countries or regions given the substantial inter-country variability observed in the participating countries. However, gynecological and drug utilization pattern data obtained in this study provides new insights into how endometriosis is managed in a real-world setting and enriches our understanding of endometriosis management across several European countries.

12. Other information

Not applicable.

13. Conclusion

On January 26, 2019, the Safety Monitoring and Advisory Council concluded after the presentation of the final INAS VIPOS results:

"At the study's end, no safety signals are evident concerning DNG. Outcome events were less common than predicted based on previous data. Anemia is not a concern, and several explanations may account for the higher rate of depression associated with DNG in a cohort study without random allocation to treatment. Depression was an uncommon outcome, and the confidence intervals around hazard ratios were wide, reflecting statistical instability. The SMAC suggested analyzing treatment discontinuations separately for lack of effectiveness vs. intolerance of side effects. As in prior meetings, the SMAC recommends that the final study report be circumspect, given the rarity of the outcomes, subjectivity of some outcomes, the potential for prescribing bias, and possible incomplete control for some confounders."

14. References

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Appendices

Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
1	Appendix 1.1		Study Protocol
2	Appendix 1.2		Protocol amendment
3	Appendix 1.3		Baseline Questionnaire
4	Appendix 1.4		Follow-up Questionnaire
3	Appendix 1.5		Statistical Analysis Plan (SAP)
6	Appendix 1.6		Volumes of Tables

Annex 2. Additional information: Tables in landscape format

Table 42: Incidence rate of clinically relevant anemia, AT population, Complete cohort

	DNG	*OAED*			*NAED*			*Ex-use*	*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*			
Number of women-years	4482	1694	750	2444	33806	5753	40090	36877	294	84187
Confirmed anemia	15	6	6	12	72	18	92	78	0	197
IR** *(95% CI)	33.5 (18.7-55.1)	35.4 (13.0-76.9)	80.0 (29.4-173.3)	49.1 (25.4-85.6)	21.3 (16.7-26.8)	31.3 (18.6-49.4)	22.9 (18.5-28.1)	21.2 (16.7-26.4)	0.0 (0.0-124.9)	23.4 (20.2-26.9)
Thereof										
Treated with iron tablets	13	3	5	8	59	16	76	64	0	161
	29.0 (15.5-49.6)	17.7 (3.7-51.7)	66.6 (21.7-154.8)	32.7 (14.1-64.4)	17.5 (13.3-22.5)	27.8 (15.9-45.1)	19.0 (14.9-23.7)	17.4 (13.4-22.2)	0.0 (0.0-124.9)	19.1 (16.3-22.3)
Treated with iron infusion/injections	2	2	0	2	12	2	14	12	0	30
	4.5 (0.54-16.1)	11.8 (1.4-42.6)	0.0 (0.0-49.0)	8.2 (0.99-29.5)	3.5 (1.8-6.2)	3.5 (0.42-12.6)	3.5 (1.9-5.9)	3.3 (1.7-5.7)	0.0 (0.0-124.9)	3.6 (2.4-5.1)
Treated with blood transfusions	0	1	1	2	1	0	2	2	0	6
	0.0 (0.0-8.2)	5.9 (0.15-32.9)	13.3 (0.34-74.0)	8.2 (0.99-29.5)	0.30 (0.007-1.6)	0.0 (0.0-6.4)	0.50 (0.06-1.8)	0.54 (0.07-2.0)	0.0 (0.0-124.9)	0.71 (0.26-1.6)

Note: *Incidence rate is shown per 10^4 women-years.

Table 43: Incidence rate of new depression or worsening of an existing depression, AT population, Complete cohort

	DNG	*OAED*			*NAED*			*Ex-use*	*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*			
Number of women-years	4482	1694	750	2444	33806	5753	40090	36877	294	84187
Confirmed depression	16	1	1	2	59	9	68	53	0	139
IR** *(95% CI)	35.7 (20.4-57.9)	5.9 (0.15-32.9)	13.3 (0.34-74.0)	8.2 (0.99-29.5)	17.5 (13.3-22.5)	15.6 (7.2-29.7)	17.0 (13.2-21.5)	14.4 (10.8-18.8)	0.0 (0.0-124.9)	16.5 (13.9-19.5)
Thereof										
Treated by psychiatrist	9	1	0	1	53	6	59	40	0	109
	20.1 (9.2-38.1)	5.9 (0.15-32.9)	0.0 (0.0-49.0)	4.1 (0.10-22.8)	15.7 (11.7-20.5)	10.4 (3.8-22.7)	14.7 (11.2-19.0)	10.8 (7.8-14.8)	0.0 (0.0-124.9)	12.9 (10.6-15.6)
Hospital admission	5	0	0	0	4	3	7	10	0	22
	11.2 (3.6-26.0)	0.0 (0.0-21.8)	0.0 (0.0-49.0)	0.0 (0.0-15.1)	1.2 (0.32-3.0)	5.2 (1.1-15.2)	1.7 (0.70-3.6)	2.7 (1.3-5.0)	0.0 (0.0-124.9)	2.6 (1.6-4.0)
Suicide attempt	2	0	1	1	2	0	2	3	0	8
	4.5 (0.54-16.1)	0.0 (0.0-21.8)	13.3 (0.34-74.0)	4.1 (0.10-22.8)	0.59 (0.07-2.1)	0.0 (0.0-6.4)	0.50 (0.06-1.8)	0.81 (0.17-2.4)	0.0 (0.0-124.9)	0.95 (0.41-1.9)
Committed suicide	0	0	0	0	0	0	0	0	0	0
	0.0 (0.0-8.2)	0.0 (0.0-21.8)	0.0 (0.0-49.0)	0.0 (0.0-15.1)	0.0 (0.0-1.1)	0.0 (0.0-6.4)	0.0 (0.0-0.92)	0.0 (0.0-1.0)	0.0 (0.0-124.9)	0.0 (0.0-0.44)
Personal history of depression**	3	1	0	1	9	4	13	7	0	24
	6.7 (1.4-19.5)	5.9 (0.15-32.9)	0.0 (0.0-49.0)	4.1 (0.10-22.8)	2.7 (1.2-5.1)	7.0 (1.9-17.8)	3.2 (1.7-5.5)	1.9 (0.76-3.9)	0.0 (0.0-124.9)	2.9 (1.8-4.2)
Family history of depression**	7	0	0	0	10	1	11	6	0	24
	15.6 (6.3-32.2)	0.0 (0.0-21.8)	0.0 (0.0-49.0)	0.0 (0.0-15.1)	3.0 (1.4-5.4)	1.7 (0.04-9.7)	2.7 (1.4-4.9)	1.6 (0.60-3.5)	0.0 (0.0-124.9)	2.9 (1.8-4.2)

Note: *Incidence rate is shown per 10^4 women-years.
** Reported at baseline

Table 44: Detailed listing of SAE occurring during DNG long- or short-term use (according to ICD10)

ICD10 Code by Organ system/group	ICD10 Label	DNG Long-term use	DNG Short-term use	Total
Infectious diseases				
A09	Infectious gastroenteritis and colitis, unspecified	1	1	2
B00.5	Herpes viral ocular disease		1	1
B54	Unspecified malaria		1	1
B99	Other and unspecified infectious diseases		1	1
Neoplasms, malignant				
C26.0	Malignant neoplasm of intestinal tract, part unspecified	1		1
C43.9	Malignant melanoma of skin, unspecified		1	1
C44.9	Malignant neoplasm of skin, unspecified		1	1
C50.4	Malignant neoplasm of upper-outer quadrant of breast	1		1
C50.9	Malignant neoplasm of breast, unspecified part	1		1
C56	Malignant neoplasm of ovary	1		1
D06.9	Carcinoma in situ of cervix, unspecified		1	1
Neoplasms, benign				
D25.9	Leiomyoma of uterus, unspecified	2	2	4
D27	Benign neoplasm of ovary		1	1
Endocrine diseases				
E14.9	Diabetes mellitus, unspecified		1	1
Mental and behavioral disorders				
F32.9	Depression	1	5	6
F41.0	Panic disorder [episodic paroxysmal anxiety] without agoraphobia	1		1
F41.2	Mixed anxiety and depressive disorder		1	1

ICD10 Code by Organ system/group	ICD10 Label	DNG Long-term use	DNG Short-term use	Total
Diseases of the nervous system				
G40.9	Epilepsy, unspecified		2	2
G43.9	Migraine, unspecified		1	1
G44.8	Other specified headache syndromes	2	1	3
G62.9	Polyneuropathy, unspecified		1	1
G93.5	Death due to cerebral compression and intracranial cyst with hemorrhage	1		1
Cardiovascular system				
I10.9	Essential (primary) hypertension, unspecified	1	1	2
I26.9	Pulmonary embolism		1	1
I42.9	Cardiomyopathy, unspecified	1		1
I51.8	Other ill-defined heart diseases	1		1
I80.2	DVT of other deep vessels of lower extremities	1		1
I80.8	DVT of other sites	1	1	2
I83.9	Varicose veins of lower extremities without ulcer or inflammation	1	2	3
R42	Dizziness and giddiness	2		2
Respiratory system				
J03.9	Acute tonsillitis, unspecified	1	1	2
J04.0	Acute laryngitis	1		1
J06.9	Acute upper respiratory infection, unspecified		5	5
J18.9	Pneumonia, unspecified organism		2	2
J34.2	Deviated nasal septum		1	1
Digestive system				
K07.6	Temporomandibular joint disorders	1		1

ICD10 Code by Organ system/group	ICD10 Label	DNG Long-term use	DNG Short-term use	Total
K11.5	Sialolithiasis	1		1
K25.9	Gastric ulcer, unspecified as acute or chronic, without hemorrhage or perforation		1	1
K26.9	Duodenal ulcer, unspecified as acute or chronic, without hemorrhage or perforation		1	1
K29.5	Chronic gastritis, unspecified	1		1
K35.9	Acute appendicitis	4	4	8
K50.0	Crohn's disease of small intestine	1	1	2
K51.9	Ulcerative colitis, unspecified		1	1
K52.9	Noninfective gastroenteritis and colitis, unspecified		1	1
K56.4	Other impaction of intestine	1		1
K56.5	Intestinal adhesions [bands] with obstruction (postprocedural) (post infection)		1	1
K61.1	Rectal abscess		2	2
K66.0	Peritoneal adhesions (postprocedural) (post infection)	1		1
K71.2	Toxic liver disease with acute hepatitis	1		1
K80.2	Calculus of gallbladder without cholecystitis		2	2
K80.20	Calculus of gallbladder without cholecystitis without obstruction		1	1
K82.9	Disease of gallbladder, unspecified	1	2	3
K85.8	Other acute pancreatitis		1	1
K85.9	Acute pancreatitis, unspecified		1	1
K92	Other diseases of digestive system		1	1
Skin				
L40.9	Psoriasis, unspecified		1	1
L59.8	Other specified disorders of the skin and subcutaneous tissue related to radiation	1		1

ICD10 Code by Organ system/group	ICD10 Label	DNG Long-term use	DNG Short-term use	Total
Musculoskeletal system and connective tissue				
M19.99	Arthrosis, unspecified, site unspecified		2	2
M42.9	Spinal osteochondrosis, unspecified		1	1
M51.2	Other specified intervertebral disc displacement	1		1
M51.9	Unspecified thoracic, thoracolumbar and lumbosacral intervertebral disc disorder		1	1
M54.2	Cervicalgia	1		1
M54.9	Dorsalgia, unspecified	1		1
M54.97	Unspecified dorsalgia, lumbosacral region		1	1
M67.44	Ganglion, hand		1	1
M99.81	Other biomechanical lesions of cervical region	1		1
Genitourinary system				
N05.9	Unspecified nephritic syndrome with unspecified morphologic changes		1	1
N10	Acute tubulo-interstitial nephritis		1	1
N64.9	Disorder of breast, unspecified		1	1
N70.1	Chronic salpingitis and oophoritis		1	1
N70.9	Salpingitis and oophoritis, unspecified		1	1
N73.6;N80.3;N80.4	Female pelvic peritoneal adhesions, endometriosis of pelvic peritoneum and rectovaginal septum and vagina	1		1
N73.6;N83.2	Female pelvic peritoneal adhesions and ovarian cysts		2	2
N73.9	Female pelvic inflammatory disease, unspecified	1		1
N75.1	Abscess of Bartholin's gland		1	1
N80.1	Endometriosis of ovary	1	5	6
N80.2; N80.5	Endometriosis of fallopian tube and intestine		1	1
N80.3; N83.2	Endometriosis of pelvic peritoneum and ovarian cysts		2	2

ICD10 Code by Organ system/group	ICD10 Label	DNG Long-term use	DNG Short-term use	Total
N80.5	Endometriosis of intestine		1	1
N80.9	Endometriosis, unspecified	1	5	6
N83.2	Other and unspecified ovarian cysts	2	12	14
N83.8	Other noninflammatory disorders of ovary, fallopian tube and broad ligament		1	1
N83.9	Noninflammatory disorder of ovary, fallopian tube and broad ligament, unspecified		1	1
N84.9	Polyp of female genital tract, unspecified		1	1
N89.8	Other specified noninflammatory disorders of vagina		1	1
N93.9	Abnormal uterine and vaginal bleeding, unspecified		5	5
N97.1	Female infertility of tubal origin		1	1
N97.9	Female infertility, unspecified		1	1
U10.9	Abdominal pain, unspecified	1	2	3
U20.9	Pain caused by endometriosis, unspecified		2	2
Pregnancy, delivery and puerperium				
O00.9	Ectopic pregnancy, unspecified		2	2
O03.9	Complete or unspecified spontaneous abortion without complication		3	3
O20.0	Threatened abortion		1	1
O20.9	Hemorrhage in early pregnancy, unspecified		1	1
Injury, poisoning, accidents etc.				
S06.0	Concussion		1	1
S42.3	Fracture of shaft of humerus		2	2
S42.9	Fracture of shoulder girdle, part unspecified		1	1
S83.3	Tear of articular cartilage of knee, current	1		1
T12.0	Fracture of lower limb, level unspecified, closed		1	1

ICD10 Code by Organ system/group	ICD10 Label	DNG Long-term use	DNG Short-term use	Total
T14.1	Open wound of unspecified body region		1	1
T14.3	Dislocation, sprain and strain of unspecified body region	1		1
T62.8	Other specified noxious substances eaten as food		1	1
T62.9	Noxious substance eaten as food, unspecified		1	1
T65.9	Toxic effect of unspecified substance	1	1	2
T75.4	Effects of electric current		1	1
T78.0	Anaphylactic shock due to adverse food reaction	1	1	2
Total		50	130	180

Table 45: Selected population characteristics, AT population

	DNG	OAED			NAED			Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED		
Number (%) of women	3023 (100%)	2542 (100%)	829 (100%)	3371 (100%)	16638 (100%)	3246 (100%)	20016 (100%)	20 (100%)	26430 (100%)
Age (years)									
Mean	35.1	37.5	35.5	37.0	30.9	36.9	31.9	37.9	32.9
SD	7.70	8.43	7.18	8.19	8.80	7.90	9.01	8.38	8.96
BMI category									
< 20	573 (19.0%)	304 (12.0%)	109 (13.1%)	413 (12.3%)	3622 (21.8%)	343 (10.6%)	3976 (19.9%)	2 (10.0%)	4964 (18.8%)
>= 20 and <25	1571 (52.0%)	1174 (46.2%)	347 (41.9%)	1521 (45.1%)	8637 (51.9%)	1610 (49.6%)	10293 (51.4%)	8 (40.0%)	13393 (50.7%)
>= 25 and <30	608 (20.1%)	855 (33.6%)	250 (30.2%)	1105 (32.8%)	3337 (20.1%)	992 (30.6%)	4368 (21.8%)	6 (30.0%)	6087 (23.0%)
>= 30 and <35	200 (6.6%)	152 (6.0%)	85 (10.3%)	237 (7.0%)	826 (5.0%)	215 (6.6%)	1065 (5.3%)	2 (10.0%)	1504 (5.7%)
>= 35	69 (2.3%)	57 (2.2%)	38 (4.6%)	95 (2.8%)	212 (1.3%)	84 (2.6%)	308 (1.5%)	2 (10.0%)	474 (1.8%)
Missing	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.0%)	2 (0.1%)	6 (0.0%)	0 (0.0%)	8 (0.0%)
Educational level									
Lower than university entrance level	654 (21.6%)	197 (7.7%)	52 (6.3%)	249 (7.4%)	3090 (18.6%)	365 (11.2%)	3466 (17.3%)	2 (10.0%)	4371 (16.5%)
University entrance level	1006 (33.3%)	698 (27.5%)	466 (56.2%)	1164 (34.5%)	6243 (37.5%)	1267 (39.0%)	7572 (37.8%)	13 (65.0%)	9755 (36.9%)
Higher than university entrance level	1363 (45.1%)	1647 (64.8%)	311 (37.5%)	1958 (58.1%)	7305 (43.9%)	1614 (49.7%)	8978 (44.9%)	5 (25.0%)	12304 (46.6%)
Current smoker	587 (19.4%)	524 (20.6%)	205 (24.7%)	729 (21.6%)	3473 (20.9%)	556 (17.1%)	4049 (20.2%)	6 (30.0%)	5371 (20.3%)
Thereof									
Heavy smoker (>15 cigarettes/day)	91 (3.0%)	215 (8.5%)	66 (8.0%)	281 (8.3%)	424 (2.5%)	119 (3.7%)	547 (2.7%)	0 (0.0%)	919 (3.5%)
Gravidity (ever pregnant)	1936 (64.0%)	1494 (58.8%)	661 (79.7%)	2155 (63.9%)	8177 (49.1%)	2090 (64.4%)	10390 (51.9%)	17 (85.0%)	14498 (54.9%)
Parity (ever live birth)	1785 (59.0%)	1403 (55.2%)	645 (77.8%)	2048 (60.8%)	7378 (44.3%)	2017 (62.1%)	9511 (47.5%)	15 (75.0%)	13359 (50.5%)
Personal history of depression	159 (5.3%)	39 (1.5%)	2 (0.2%)	41 (1.2%)	318 (1.9%)	103 (3.2%)	423 (2.1%)	1 (5.0%)	624 (2.4%)
Personal history of anemia	196 (6.5%)	103 (4.1%)	12 (1.4%)	115 (3.4%)	899 (5.4%)	266 (8.2%)	1174 (5.9%)	2 (10.0%)	1487 (5.6%)
Use of Antidepressants/SSRI	33 (1.1%)	13 (0.5%)	1 (0.1%)	14 (0.4%)	48 (0.3%)	14 (0.4%)	62 (0.3%)	0 (0.0%)	109 (0.4%)

Table 46: Selected population characteristics at study entry, Germany only, AT population

	DNG	OAED			NAED			Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED		
Number (%) of women	454 (100%)	75 (100%)	0 (0.0%)	75 (100%)	871 (100%)	313 (100%)	1187 (100%)	1 (100%)	1717 (100%)
Age (years)									
Mean	35.7	36.6		36.6	26.7	34.9	28.9	32.1	31.1
SD	9.09	7.77		7.77	8.54	9.05	9.42		9.79
BMI category									
< 20	79 (17.4%)	14 (18.7%)	0 (0.0%)	14 (18.7%)	193 (22.2%)	45 (14.4%)	239 (20.1%)	0 (0.0%)	332 (19.3%)
>= 20 and <25	219 (48.2%)	32 (42.7%)	0 (0.0%)	32 (42.7%)	445 (51.1%)	136 (43.5%)	582 (49.0%)	1 (100%)	834 (48.6%)
>= 25 and <30	89 (19.6%)	18 (24.0%)	0 (0.0%)	18 (24.0%)	158 (18.1%)	76 (24.3%)	235 (19.8%)	0 (0.0%)	342 (19.9%)
>= 30 and <35	42 (9.3%)	7 (9.3%)	0 (0.0%)	7 (9.3%)	48 (5.5%)	39 (12.5%)	87 (7.3%)	0 (0.0%)	136 (7.9%)
>= 35	24 (5.3%)	4 (5.3%)	0 (0.0%)	4 (5.3%)	25 (2.9%)	17 (5.4%)	42 (3.5%)	0 (0.0%)	70 (4.1%)
Missing	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	3 (0.2%)
Educational level									
Lower than university entrance level	313 (68.9%)	42 (56.0%)	0 (0.0%)	42 (56.0%)	576 (66.1%)	237 (75.7%)	816 (68.7%)	0 (0.0%)	1171 (68.2%)
University entrance level	60 (13.2%)	11 (14.7%)	0 (0.0%)	11 (14.7%)	173 (19.9%)	46 (14.7%)	219 (18.4%)	0 (0.0%)	290 (16.9%)
Higher than university entrance level	81 (17.8%)	22 (29.3%)	0 (0.0%)	22 (29.3%)	122 (14.0%)	30 (9.6%)	152 (12.8%)	1 (100%)	256 (14.9%)
Current smoker	137 (30.2%)	25 (33.3%)	0 (0.0%)	25 (33.3%)	262 (30.1%)	137 (43.8%)	401 (33.8%)	1 (100%)	564 (32.8%)
Thereof									
Heavy smoker (>15 cigarettes/day)	29 (6.4%)	5 (6.7%)	0 (0.0%)	5 (6.7%)	30 (3.4%)	34 (10.9%)	65 (5.5%)	0 (0.0%)	99 (5.8%)
Gravidity (ever pregnant)	254 (55.9%)	42 (56.0%)	0 (0.0%)	42 (56.0%)	310 (35.6%)	224 (71.6%)	537 (45.2%)	1 (100%)	834 (48.6%)
Parity (ever live birth)	228 (50.2%)	35 (46.7%)	0 (0.0%)	35 (46.7%)	269 (30.9%)	206 (65.8%)	477 (40.2%)	0 (0.0%)	740 (43.1%)
Personal history of depression	72 (15.9%)	17 (22.7%)	0 (0.0%)	17 (22.7%)	55 (6.3%)	32 (10.2%)	87 (7.3%)	0 (0.0%)	176 (10.3%)
Personal history of anemia	27 (5.9%)	11 (14.7%)	0 (0.0%)	11 (14.7%)	37 (4.2%)	20 (6.4%)	57 (4.8%)	0 (0.0%)	95 (5.5%)
Use of Antidepressants/SSRI	17 (3.7%)	4 (5.3%)	0 (0.0%)	4 (5.3%)	11 (1.3%)	7 (2.2%)	18 (1.5%)	0 (0.0%)	39 (2.3%)

Table 47: Selected population characteristics at study entry, Poland only, AT population

	DNG	OAED			NAED			Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED		
Number (%) of women	525 (100%)	10 (100%)	75 (100%)	85 (100%)	303 (100%)	36 (100%)	342 (100%)	2 (100%)	954 (100%)
Age (years)									
Mean	31.9	30.9	32.3	32.1	30.7	32.0	31.0	26.7	31.6
SD	7.34	5.26	8.41	8.09	8.91	8.10	8.98	3.05	8.03
BMI category									
< 20	128 (24.4%)	1 (10.0%)	16 (21.3%)	17 (20.0%)	91 (30.0%)	13 (36.1%)	104 (30.4%)	0 (0.0%)	249 (26.1%)
>= 20 and <25	269 (51.2%)	8 (80.0%)	33 (44.0%)	41 (48.2%)	147 (48.5%)	17 (47.2%)	164 (48.0%)	1 (50.0%)	475 (49.8%)
>= 25 and <30	98 (18.7%)	1 (10.0%)	21 (28.0%)	22 (25.9%)	51 (16.8%)	6 (16.7%)	59 (17.3%)	1 (50.0%)	180 (18.9%)
>= 30 and <35	24 (4.6%)	0 (0.0%)	4 (5.3%)	4 (4.7%)	13 (4.3%)	0 (0.0%)	13 (3.8%)	0 (0.0%)	41 (4.3%)
>= 35	5 (1.0%)	0 (0.0%)	1 (1.3%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	7 (0.7%)
Missing	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	2 (0.2%)
Educational level									
Lower than university entrance level	87 (16.6%)	1 (10.0%)	10 (13.3%)	11 (12.9%)	24 (7.9%)	2 (5.6%)	27 (7.9%)	0 (0.0%)	125 (13.1%)
University entrance level	213 (40.6%)	4 (40.0%)	39 (52.0%)	43 (50.6%)	127 (41.9%)	14 (38.9%)	142 (41.5%)	1 (50.0%)	399 (41.8%)
Higher than university entrance level	225 (42.9%)	5 (50.0%)	26 (34.7%)	31 (36.5%)	152 (50.2%)	20 (55.6%)	173 (50.6%)	1 (50.0%)	430 (45.1%)
Current smoker	100 (19.0%)	1 (10.0%)	14 (18.7%)	15 (17.6%)	68 (22.4%)	8 (22.2%)	77 (22.5%)	2 (100%)	194 (20.3%)
Thereof									
Heavy smoker (>15 cigarettes/day)	14 (2.7%)	0 (0.0%)	2 (2.7%)	2 (2.4%)	7 (2.3%)	1 (2.8%)	8 (2.3%)	0 (0.0%)	24 (2.5%)
Gravidity (ever pregnant)	309 (58.9%)	2 (20.0%)	47 (62.7%)	49 (57.6%)	138 (45.5%)	12 (33.3%)	153 (44.7%)	0 (0.0%)	511 (53.6%)
Parity (ever live birth)	291 (55.4%)	2 (20.0%)	45 (60.0%)	47 (55.3%)	134 (44.2%)	12 (33.3%)	149 (43.6%)	0 (0.0%)	487 (51.0%)
Personal history of depression	27 (5.1%)	0 (0.0%)	1 (1.3%)	1 (1.2%)	11 (3.6%)	2 (5.6%)	13 (3.8%)	0 (0.0%)	41 (4.3%)
Personal history of anemia	28 (5.3%)	0 (0.0%)	1 (1.3%)	1 (1.2%)	13 (4.3%)	2 (5.6%)	15 (4.4%)	0 (0.0%)	44 (4.6%)
Use of Antidepressants/SSRI	3 (0.6%)	0 (0.0%)	1 (1.3%)	1 (1.2%)	4 (1.3%)	2 (5.6%)	6 (1.8%)	0 (0.0%)	10 (1.0%)

Table 48: Selected population characteristics at study entry, Hungary only, AT population

	DNG	OAED			NAED			Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED		
Number (%) of women	631 (100%)	410 (100%)	0 (0.0%)	410 (100%)	6980 (100%)	241 (100%)	7246 (100%)	0 (0.0%)	8287 (100%)
Age (years)									
Mean	33.3	33.4		33.4	26.3	34.9	26.7		27.5
SD	6.14	6.24		6.24	7.04	8.65	7.36		7.55
BMI category									
< 20	194 (30.7%)	110 (26.8%)	0 (0.0%)	110 (26.8%)	2141 (30.7%)	40 (16.6%)	2183 (30.1%)	0 (0.0%)	2487 (30.0%)
>= 20 and <25	296 (46.9%)	215 (52.4%)	0 (0.0%)	215 (52.4%)	3847 (55.1%)	118 (49.0%)	3976 (54.9%)	0 (0.0%)	4487 (54.1%)
>= 25 and <30	95 (15.1%)	59 (14.4%)	0 (0.0%)	59 (14.4%)	745 (10.7%)	63 (26.1%)	816 (11.3%)	0 (0.0%)	970 (11.7%)
>= 30 and <35	38 (6.0%)	15 (3.7%)	0 (0.0%)	15 (3.7%)	188 (2.7%)	15 (6.2%)	204 (2.8%)	0 (0.0%)	257 (3.1%)
>= 35	8 (1.3%)	11 (2.7%)	0 (0.0%)	11 (2.7%)	58 (0.8%)	4 (1.7%)	65 (0.9%)	0 (0.0%)	84 (1.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.4%)	2 (0.0%)	0 (0.0%)	2 (0.0%)
Educational level									
Lower than university entrance level	210 (33.3%)	141 (34.4%)	0 (0.0%)	141 (34.4%)	2430 (34.8%)	87 (36.1%)	2524 (34.8%)	0 (0.0%)	2875 (34.7%)
University entrance level	129 (20.4%)	75 (18.3%)	0 (0.0%)	75 (18.3%)	2557 (36.6%)	102 (42.3%)	2673 (36.9%)	0 (0.0%)	2877 (34.7%)
Higher than university entrance level	292 (46.3%)	194 (47.3%)	0 (0.0%)	194 (47.3%)	1993 (28.6%)	52 (21.6%)	2049 (28.3%)	0 (0.0%)	2535 (30.6%)
Current smoker	136 (21.6%)	85 (20.7%)	0 (0.0%)	85 (20.7%)	1906 (27.3%)	55 (22.8%)	1964 (27.1%)	0 (0.0%)	2185 (26.4%)
Thereof									
Heavy smoker (>15 cigarettes/day)	16 (2.5%)	11 (2.7%)	0 (0.0%)	11 (2.7%)	244 (3.5%)	12 (5.0%)	257 (3.5%)	0 (0.0%)	284 (3.4%)
Gravidity (ever pregnant)	262 (41.5%)	134 (32.7%)	0 (0.0%)	134 (32.7%)	1979 (28.4%)	197 (81.7%)	2199 (30.3%)	0 (0.0%)	2595 (31.3%)
Parity (ever live birth)	207 (32.8%)	108 (26.3%)	0 (0.0%)	108 (26.3%)	1454 (20.8%)	193 (80.1%)	1668 (23.0%)	0 (0.0%)	1983 (23.9%)
Personal history of depression	31 (4.9%)	14 (3.4%)	0 (0.0%)	14 (3.4%)	164 (2.3%)	11 (4.6%)	176 (2.4%)	0 (0.0%)	221 (2.7%)
Personal history of anemia	21 (3.3%)	14 (3.4%)	0 (0.0%)	14 (3.4%)	364 (5.2%)	16 (6.6%)	380 (5.2%)	0 (0.0%)	415 (5.0%)
Use of Antidepressants/SSRI	10 (1.6%)	9 (2.2%)	0 (0.0%)	9 (2.2%)	30 (0.4%)	1 (0.4%)	31 (0.4%)	0 (0.0%)	50 (0.6%)

Table 49: Selected population characteristics at study entry, Switzerland only, AT population

	DNG	OAED			NAED			Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED		
Number (%) of women	62 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (100%)	4 (100%)	12 (100%)	0 (0.0%)	74 (100%)
Age (years)									
Mean	30.8				27.2	24.6	26.4		30.1
SD	7.19				5.14	2.35	4.47		6.99
BMI category									
< 20	18 (29.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (37.5%)	1 (25.0%)	4 (33.3%)	0 (0.0%)	22 (29.7%)
>= 20 and <25	27 (43.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (62.5%)	1 (25.0%)	6 (50.0%)	0 (0.0%)	33 (44.6%)
>= 25 and <30	10 (16.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	1 (8.3%)	0 (0.0%)	11 (14.9%)
>= 30 and <35	6 (9.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (8.1%)
>= 35	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	1 (8.3%)	0 (0.0%)	2 (2.7%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Educational level									
Lower than university entrance level	32 (51.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (37.5%)	4 (100%)	7 (58.3%)	0 (0.0%)	39 (52.7%)
University entrance level	11 (17.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	12 (16.2%)
Higher than university entrance level	19 (30.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (50.0%)	0 (0.0%)	4 (33.3%)	0 (0.0%)	23 (31.1%)
Current smoker	15 (24.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (37.5%)	3 (75.0%)	6 (50.0%)	0 (0.0%)	21 (28.4%)
Thereof									
Heavy smoker (>15 cigarettes/day)	6 (9.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	7 (9.5%)
Gravidity (ever pregnant)	10 (16.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	2 (50.0%)	3 (25.0%)	0 (0.0%)	13 (17.6%)
Parity (ever live birth)	7 (11.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (9.5%)
Personal history of depression	8 (12.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)	3 (75.0%)	5 (41.7%)	0 (0.0%)	13 (17.6%)
Personal history of anemia	7 (11.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (25.0%)	2 (16.7%)	0 (0.0%)	9 (12.2%)
Use of Antidepressants/SSRI	3 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	2 (50.0%)	3 (25.0%)	0 (0.0%)	6 (8.1%)

Table 50: Selected population characteristics at study entry, Russia only, AT population

	DNG	OAED			NAED			Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED		
Number (%) of women	1039 (100%)	1778 (100%)	234 (100%)	2012 (100%)	7753 (100%)	2120 (100%)	9957 (100%)	0 (0.0%)	13008 (100%)
Age (years)									
Mean	37.0	38.7	36.0	38.4	35.0	36.8	35.5		36.0
SD	7.10	8.53	5.91	8.31	8.11	7.52	8.08		8.12
BMI category									
< 20	114 (11.0%)	137 (7.7%)	20 (8.5%)	157 (7.8%)	1065 (13.7%)	180 (8.5%)	1251 (12.6%)	0 (0.0%)	1522 (11.7%)
>= 20 and <25	605 (58.2%)	804 (45.2%)	103 (44.0%)	907 (45.1%)	3834 (49.5%)	1112 (52.5%)	4977 (50.0%)	0 (0.0%)	6489 (49.9%)
>= 25 and <30	247 (23.8%)	700 (39.4%)	96 (41.0%)	796 (39.6%)	2222 (28.7%)	692 (32.6%)	2938 (29.5%)	0 (0.0%)	3981 (30.6%)
>= 30 and <35	54 (5.2%)	106 (6.0%)	13 (5.6%)	119 (5.9%)	522 (6.7%)	97 (4.6%)	640 (6.4%)	0 (0.0%)	813 (6.3%)
>= 35	19 (1.8%)	31 (1.7%)	2 (0.9%)	33 (1.6%)	110 (1.4%)	39 (1.8%)	151 (1.5%)	0 (0.0%)	203 (1.6%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Educational level									
Lower than university entrance level	6 (0.6%)	11 (0.6%)	1 (0.4%)	12 (0.6%)	45 (0.6%)	20 (0.9%)	65 (0.7%)	0 (0.0%)	83 (0.6%)
University entrance level	442 (42.5%)	497 (28.0%)	89 (38.0%)	586 (29.1%)	3043 (39.2%)	858 (40.5%)	3938 (39.6%)	0 (0.0%)	4966 (38.2%)
Higher than university entrance level	591 (56.9%)	1270 (71.4%)	144 (61.5%)	1414 (70.3%)	4665 (60.2%)	1242 (58.6%)	5954 (59.8%)	0 (0.0%)	7959 (61.2%)
Current smoker	141 (13.6%)	385 (21.7%)	98 (41.9%)	483 (24.0%)	1113 (14.4%)	291 (13.7%)	1418 (14.2%)	0 (0.0%)	2042 (15.7%)
Thereof									
Heavy smoker (>15 cigarettes/day)	14 (1.3%)	199 (11.2%)	58 (24.8%)	257 (12.8%)	131 (1.7%)	65 (3.1%)	198 (2.0%)	0 (0.0%)	469 (3.6%)
Gravidity (ever pregnant)	854 (82.2%)	1114 (62.7%)	170 (72.6%)	1284 (63.8%)	5151 (66.4%)	1169 (55.1%)	6397 (64.2%)	0 (0.0%)	8535 (65.6%)
Parity (ever live birth)	823 (79.2%)	1069 (60.1%)	168 (71.8%)	1237 (61.5%)	4961 (64.0%)	1141 (53.8%)	6176 (62.0%)	0 (0.0%)	8236 (63.3%)
Personal history of depression	13 (1.3%)	6 (0.3%)	0 (0.0%)	6 (0.3%)	64 (0.8%)	39 (1.8%)	104 (1.0%)	0 (0.0%)	123 (0.9%)
Personal history of anemia	86 (8.3%)	68 (3.8%)	6 (2.6%)	74 (3.7%)	427 (5.5%)	178 (8.4%)	613 (6.2%)	0 (0.0%)	773 (5.9%)
Use of Antidepressants/SSRI	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	2 (0.1%)	3 (0.0%)	0 (0.0%)	3 (0.0%)

Table 51: Selected population characteristics at study entry, Ukraine only, AT population

	DNG	OAED			NAED			Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED		
Number (%) of women	312 (100%)	269 (100%)	520 (100%)	789 (100%)	723 (100%)	532 (100%)	1272 (100%)	17 (100%)	2390 (100%)
Age (years)									
Mean	37.2	36.4	35.8	36.0	35.3	39.8	37.3	39.5	36.9
SD	8.10	8.74	7.41	7.89	7.56	7.34	7.83	7.88	7.91
BMI category									
< 20	40 (12.8%)	42 (15.6%)	73 (14.0%)	115 (14.6%)	129 (17.8%)	64 (12.0%)	195 (15.3%)	2 (11.8%)	352 (14.7%)
>= 20 and <25	155 (49.7%)	115 (42.8%)	211 (40.6%)	326 (41.3%)	359 (49.7%)	226 (42.5%)	588 (46.2%)	6 (35.3%)	1075 (45.0%)
>= 25 and <30	69 (22.1%)	77 (28.6%)	133 (25.6%)	210 (26.6%)	161 (22.3%)	154 (28.9%)	319 (25.1%)	5 (29.4%)	603 (25.2%)
>= 30 and <35	36 (11.5%)	24 (8.9%)	68 (13.1%)	92 (11.7%)	55 (7.6%)	64 (12.0%)	121 (9.5%)	2 (11.8%)	251 (10.5%)
>= 35	12 (3.8%)	11 (4.1%)	35 (6.7%)	46 (5.8%)	19 (2.6%)	23 (4.3%)	48 (3.8%)	2 (11.8%)	108 (4.5%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Educational level									
Lower than university entrance level	6 (1.9%)	2 (0.7%)	41 (7.9%)	43 (5.4%)	12 (1.7%)	15 (2.8%)	27 (2.1%)	2 (11.8%)	78 (3.3%)
University entrance level	151 (48.4%)	111 (41.3%)	338 (65.0%)	449 (56.9%)	342 (47.3%)	247 (46.4%)	599 (47.1%)	12 (70.6%)	1211 (50.7%)
Higher than university entrance level	155 (49.7%)	156 (58.0%)	141 (27.1%)	297 (37.6%)	369 (51.0%)	270 (50.8%)	646 (50.8%)	3 (17.6%)	1101 (46.1%)
Current smoker	58 (18.6%)	28 (10.4%)	93 (17.9%)	121 (15.3%)	121 (16.7%)	62 (11.7%)	183 (14.4%)	3 (17.6%)	365 (15.3%)
Thereof									
Heavy smoker (>15 cigarettes/day)	12 (3.8%)	0 (0.0%)	6 (1.2%)	6 (0.8%)	11 (1.5%)	7 (1.3%)	18 (1.4%)	0 (0.0%)	36 (1.5%)
Gravidity (ever pregnant)	247 (79.2%)	202 (75.1%)	444 (85.4%)	646 (81.9%)	598 (82.7%)	486 (91.4%)	1101 (86.6%)	16 (94.1%)	2010 (84.1%)
Parity (ever live birth)	229 (73.4%)	189 (70.3%)	432 (83.1%)	621 (78.7%)	560 (77.5%)	465 (87.4%)	1041 (81.8%)	15 (88.2%)	1906 (79.7%)
Personal history of depression	8 (2.6%)	2 (0.7%)	1 (0.2%)	3 (0.4%)	22 (3.0%)	16 (3.0%)	38 (3.0%)	1 (5.9%)	50 (2.1%)
Personal history of anemia	27 (8.7%)	10 (3.7%)	5 (1.0%)	15 (1.9%)	57 (7.9%)	49 (9.2%)	107 (8.4%)	2 (11.8%)	151 (6.3%)
Use of Antidepressants/SSRI	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)

Table 52: Classification of endometriosis diagnosis at study entry, AT population

	DNG	*OAED*			*NAED*			*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*		
Number (%) of women	3023 (100%)	2542 (100%)	829 (100%)	3371 (100%)	16638 (100%)	3246 (100%)	20016 (100%)	20 (100%)	26430 (100%)
Diagnosis classification									
Diagnosis based on clinical symptoms	1608 (53.2%)	1747 (68.7%)	797 (96.1%)	2544 (75.5%)	15974 (96.0%)	2967 (91.4%)	19057 (95.2%)	18 (90.0%)	23227 (87.9%)
Diagnosis confirmed by surgery	1415 (46.8%)	795 (31.3%)	32 (3.9%)	827 (24.5%)	664 (4.0%)	279 (8.6%)	959 (4.8%)	2 (10.0%)	3203 (12.1%)

Table 53: Classification of endometriosis diagnosis at study entry, Germany only, AT population

	DNG	*OAED*			*NAED*			*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*		
Number (%) of women	454 (100%)	75 (100%)	0 (0.0%)	75 (100%)	871 (100%)	313 (100%)	1187 (100%)	1 (100%)	1717 (100%)
Diagnosis classification									
Diagnosis based on clinical symptoms	105 (23.1%)	12 (16.0%)	0 (0.0%)	12 (16.0%)	716 (82.2%)	231 (73.8%)	948 (79.9%)	1 (100%)	1066 (62.1%)
Diagnosis confirmed by surgery	349 (76.9%)	63 (84.0%)	0 (0.0%)	63 (84.0%)	155 (17.8%)	82 (26.2%)	239 (20.1%)	0 (0.0%)	651 (37.9%)

Table 54: Classification of endometriosis diagnosis at study entry, Poland only, AT population

	DNG	*OAED*			*NAED*			*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*		
Number (%) of women	525 (100%)	10 (100%)	75 (100%)	85 (100%)	303 (100%)	36 (100%)	342 (100%)	2 (100%)	954 (100%)
Diagnosis classification									
Diagnosis based on clinical symptoms	273 (52.0%)	0 (0.0%)	59 (78.7%)	59 (69.4%)	261 (86.1%)	14 (38.9%)	278 (81.3%)	1 (50.0%)	611 (64.0%)
Diagnosis confirmed by surgery	252 (48.0%)	10 (100%)	16 (21.3%)	26 (30.6%)	42 (13.9%)	22 (61.1%)	64 (18.7%)	1 (50.0%)	343 (36.0%)

Table 55: Classification of endometriosis diagnosis at study entry, Hungary only, AT population

	DNG	*OAED*			*NAED*			*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*		
Number (%) of women	631 (100%)	410 (100%)	0 (0.0%)	410 (100%)	6980 (100%)	241 (100%)	7246 (100%)	0 (0.0%)	8287 (100%)
Diagnosis classification									
Diagnosis based on clinical symptoms	28 (4.4%)	11 (2.7%)	0 (0.0%)	11 (2.7%)	6948 (99.5%)	240 (99.6%)	7212 (99.5%)	0 (0.0%)	7251 (87.5%)
Diagnosis confirmed by surgery	603 (95.6%)	399 (97.3%)	0 (0.0%)	399 (97.3%)	32 (0.5%)	1 (0.4%)	34 (0.5%)	0 (0.0%)	1036 (12.5%)

Table 56: Classification of endometriosis diagnosis at study entry, Russia only, AT population

	DNG	*OAED*			*NAED*			*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*		
Number (%) of women	1039 (100%)	1778 (100%)	234 (100%)	2012 (100%)	7753 (100%)	2120 (100%)	9957 (100%)	0 (0.0%)	13008 (100%)
Diagnosis classification									
Diagnosis based on clinical symptoms	935 (90.0%)	1533 (86.2%)	229 (97.9%)	1762 (87.6%)	7432 (95.9%)	2039 (96.2%)	9545 (95.9%)	0 (0.0%)	12242 (94.1%)
Diagnosis confirmed by surgery	104 (10.0%)	245 (13.8%)	5 (2.1%)	250 (12.4%)	321 (4.1%)	81 (3.8%)	412 (4.1%)	0 (0.0%)	766 (5.9%)

Table 57: Classification of endometriosis diagnosis at study entry, Switzerland only, AT population

	DNG	*OAED*			*NAED*			*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*		
Number (%) of women	62 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (100%)	4 (100%)	12 (100%)	0 (0.0%)	74 (100%)
Diagnosis classification									
Diagnosis based on clinical symptoms	19 (30.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (37.5%)	3 (75.0%)	6 (50.0%)	0 (0.0%)	25 (33.8%)
Diagnosis confirmed by surgery	43 (69.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (62.5%)	1 (25.0%)	6 (50.0%)	0 (0.0%)	49 (66.2%)

Table 58: Classification of endometriosis diagnosis at study entry, Ukraine only, AT population

	DNG	*OAED*			*NAED*			*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*		
Number (%) of women	312 (100%)	269 (100%)	520 (100%)	789 (100%)	723 (100%)	532 (100%)	1272 (100%)	17 (100%)	2390 (100%)
Diagnosis classification									
Diagnosis based on clinical symptoms	248 (79.5%)	191 (71.0%)	509 (97.9%)	700 (88.7%)	614 (84.9%)	440 (82.7%)	1068 (84.0%)	16 (94.1%)	2032 (85.0%)
Diagnosis confirmed by surgery	64 (20.5%)	78 (29.0%)	11 (2.1%)	89 (11.3%)	109 (15.1%)	92 (17.3%)	204 (16.0%)	1 (5.9%)	358 (15.0%)

Table 59: Incidence rate of self-reported anemia, AT population

	DNG	*OAED*			*NAED*			*Ex-use*	*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*			
Number of women-years	4482	1694	750	2444	33806	5753	40090	36877	294	84187
Self-reported anemia	69 154.0 (120.0-194.4)	26 153.5 (100.5-224.1)	12 159.9 (82.9-277.7)	38 155.5 (110.3-212.8)	297 87.9 (78.2-98.4)	86 149.5 (119.7-184.3)	389 97.0 (87.7-107.1)	458 124.2 (113.1-136.0)	4 136.2 (37.2-345.2)	958 113.8 (106.7-121.2)
Thereof										
Confirmed	15 33.5 (18.7-55.1)	6 35.4 (13.0-76.9)	6 80.0 (29.4-173.3)	12 49.1 (25.4-85.6)	72 21.3 (16.7-26.8)	18 31.3 (18.6-49.4)	92 22.9 (18.5-28.1)	78 21.2 (16.7-26.4)	0 0.0 (0.0-124.9)	197 23.4 (20.2-26.9)
Not confirmed	54 120.5 (90.6-156.9)	20 118.1 (72.3-181.8)	6 80.0 (29.4-173.3)	26 106.4 (69.6-155.5)	225 66.6 (58.2-75.8)	68 118.2 (91.9-149.6)	297 74.1 (65.9-83.0)	380 103.0 (93.0-113.9)	4 136.2 (37.2-345.2)	761 90.4 (84.1-97.0)
Recurrent anemia	20 44.6 (27.3-68.8)	7 41.3 (16.6-85.0)	1 13.3 (0.34-74.0)	8 32.7 (14.1-64.4)	85 25.1 (20.1-31.1)	31 53.9 (36.6-76.4)	116 28.9 (23.9-34.7)	83 22.5 (17.9-27.9)	0 0.0 (0.0-124.9)	227 27.0 (23.6-30.7)
Potential anemia, no further clarification possible	8 17.9 (7.7-35.1)	3 17.7 (3.7-51.7)	1 13.3 (0.34-74.0)	4 16.4 (4.5-41.9)	27 8.0 (5.3-11.6)	7 12.2 (4.9-25.1)	34 8.5 (5.9-11.8)	36 9.8 (6.8-13.5)	3 102.2 (21.1-295.7)	85 10.1 (8.1-12.5)
Anemia caused by other reason (other primary disease, surgery etc.)	9 20.1 (9.2-38.1)	2 11.8 (1.4-42.6)	0 0.0 (0.0-49.0)	2 8.2 (0.99-29.5)	27 8.0 (5.3-11.6)	7 12.2 (4.9-25.1)	36 9.0 (6.3-12.4)	154 41.8 (35.4-48.9)	0 0.0 (0.0-124.9)	201 23.9 (20.7-27.4)
Not treated by HCP	10 22.3 (10.7-41.0)	4 23.6 (6.4-60.4)	3 40.0 (8.3-116.4)	7 28.6 (11.5-58.9)	55 16.3 (12.3-21.2)	8 13.9 (6.0-27.4)	65 16.2 (12.5-20.7)	65 17.6 (13.6-22.5)	0 0.0 (0.0-124.9)	147 17.5 (14.8-20.5)
'No event'-before study, repetition	6 13.4 (4.9-29.1)	4 23.6 (6.4-60.4)	0 0.0 (0.0-49.0)	4 16.4 (4.5-41.9)	18 5.3 (3.2-8.4)	13 22.6 (12.0-38.6)	31 7.7 (5.3-11.0)	28 7.6 (5.0-11.0)	1 34.1 (0.86-188.3)	70 8.3 (6.5-10.5)
Anemia not confirmed by diagnostic measures	1 2.2 (0.06-12.4)	0 0.0 (0.0-21.8)	1 13.3 (0.34-74.0)	1 4.1 (0.10-22.8)	13 3.8 (2.0-6.6)	2 3.5 (0.42-12.6)	15 3.7 (2.1-6.2)	14 3.8 (2.1-6.4)	0 0.0 (0.0-124.9)	31 3.7 (2.5-5.2)

Note: *Incidence rate is shown per 10^4 WY.

Table 60: Incidence rate of self-reported depression, AT population

	DNG	OAED			NAED			Ex-use	Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED			
Number of women-years	4482	1694	750	2444	33806	5753	40090	36877	294	84187
Self-reported depression	165 368.2 (314.9-427.5)	29 171.2 (115.0-245.0)	17 226.6 (132.5-360.3)	46 188.2 (138.1-250.3)	334 98.8 (88.5-109.9)	97 168.6 (136.9-205.3)	433 108.0 (98.1-118.6)	315 85.4 (76.3-95.3)	2 68.1 (8.3-243.9)	961 114.2 (107.1-121.6)
Thereof										
Confirmed	16 35.7 (20.4-57.9)	1 5.9 (0.15-32.9)	1 13.3 (0.34-74.0)	2 8.2 (0.99-29.5)	59 17.5 (13.3-22.5)	9 15.6 (7.2-29.7)	68 17.0 (13.2-21.5)	53 14.4 (10.8-18.8)	0 0.0 (0.0-124.9)	139 16.5 (13.9-19.5)
Not confirmed	149 332.5 (281.9-389.2)	28 165.3 (110.1-238.1)	16 213.3 (122.4-344.0)	44 180.0 (131.1-240.9)	275 81.3 (72.0-91.5)	88 153.0 (122.9-188.1)	365 91.0 (82.0-100.8)	262 71.0 (62.7-80.2)	2 68.1 (8.3-243.9)	822 97.6 (91.1-104.5)
Recurrent depression	31 69.2 (47.0-98.0)	1 5.9 (0.15-32.9)	1 13.3 (0.34-74.0)	2 8.2 (0.99-29.5)	43 12.7 (9.2-17.1)	11 19.1 (9.5-34.2)	54 13.5 (10.1-17.6)	38 10.3 (7.3-14.1)	0 0.0 (0.0-124.9)	125 14.8 (12.4-17.7)
Potential depression, no further clarification possible	12 26.8 (13.8-46.7)	4 23.6 (6.4-60.4)	3 40.0 (8.3-116.4)	7 28.6 (11.5-58.9)	31 9.2 (6.2-13.0)	14 24.3 (13.3-40.8)	46 11.5 (8.4-15.3)	44 11.9 (8.7-16.0)	1 34.1 (0.86-188.3)	110 13.1 (10.7-15.7)
Depression treated by GP	27 60.2 (39.7-87.5)	3 17.7 (3.7-51.7)	4 53.3 (14.5-135.9)	7 28.6 (11.5-58.9)	41 12.1 (8.7-16.4)	9 15.6 (7.2-29.7)	50 12.5 (9.3-16.4)	27 7.3 (4.8-10.7)	0 0.0 (0.0-124.9)	111 13.2 (10.8-15.9)
Depressive disorders treated by psychologist	11 24.5 (12.3-43.9)	3 17.7 (3.7-51.7)	1 13.3 (0.34-74.0)	4 16.4 (4.5-41.9)	29 8.6 (5.7-12.3)	11 19.1 (9.5-34.2)	40 10.0 (7.1-13.6)	12 3.3 (1.7-5.7)	0 0.0 (0.0-124.9)	67 8.0 (6.2-10.1)
Other psychiatric disorders (bipolar, anxiety, eating disorders)	3 6.7 (1.4-19.5)	1 5.9 (0.15-32.9)	0 0.0 (0.0-49.0)	1 4.1 (0.10-22.8)	33 9.8 (6.7-13.7)	5 8.7 (2.8-20.3)	38 9.5 (6.7-13.0)	19 5.2 (3.1-8.0)	1 34.1 (0.86-188.3)	62 7.4 (5.6-9.4)
Other psychiatric problems (mood changes, psychosomatic disorders)	24 53.6 (34.3-79.6)	11 64.9 (32.5-115.9)	5 66.6 (21.7-154.8)	16 65.5 (37.5-106.1)	57 16.9 (12.8-21.8)	21 36.5 (22.6-55.7)	79 19.7 (15.6-24.6)	70 19.0 (14.8-24.0)	0 0.0 (0.0-124.9)	189 22.5 (19.4-25.9)
'No event'-before study, repetition	41 91.5 (65.7-123.9)	5 29.5 (9.6-68.8)	2 26.7 (3.2-96.0)	7 28.6 (11.5-58.9)	41 12.1 (8.7-16.4)	17 29.6 (17.2-47.3)	58 14.5 (11.0-18.7)	52 14.1 (10.5-18.5)	0 0.0 (0.0-124.9)	158 18.8 (16.0-21.9)

Note: *Incidence rate is shown per 10^4 WY.

Table 61: Incidence rate of serious adverse events by organ system, AT population

	DNG	*OAED*			*NAED*			*Ex-use*	*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*			
Number of women-years*	4482	1694	750	2444	33806	5753	40090	36877	294	84187
Serious adverse events**	180	79	41	120	881	254	1163	1405	4	2872
IR* *(95% CI)*	401.6 (346.0-463.3)	466.4 (371.0-578.0)	546.5 (395.0-734.1)	491.0 (408.8-584.3)	260.6 (243.9-278.2)	441.5 (389.9-497.9)	290.1 (273.9-307.0)	381.0 (361.7-401.0)	136.2 (37.2-345.2)	341.1 (329.0-353.6)
Thereof										
Infectious diseases	5 11.2 (3.6-26.0)	1 5.9 (0.15-32.9)	0 0.0 (0.0-49.0)	1 4.1 (0.10-22.8)	43 12.7 (9.2-17.1)	5 8.7 (2.8-20.3)	48 12.0 (8.8-15.9)	30 8.1 (5.5-11.6)	1 34.1 (0.86-188.3)	85 10.1 (8.1-12.5)
Neoplasms, malignant	7 15.6 (6.3-32.2)	3 17.7 (3.7-51.7)	1 13.3 (0.34-74.0)	4 16.4 (4.5-41.9)	25 7.4 (4.8-10.9)	8 13.9 (6.0-27.4)	34 8.5 (5.9-11.8)	63 17.1 (13.1-21.9)	0 0.0 (0.0-124.9)	108 12.8 (10.5-15.5)
Neoplasms, benign	5 11.2 (3.6-26.0)	2 11.8 (1.4-42.6)	1 13.3 (0.34-74.0)	3 12.3 (2.5-35.8)	12 3.5 (1.8-6.2)	9 15.6 (7.2-29.7)	23 5.7 (3.6-8.6)	20 5.4 (3.3-8.4)	0 0.0 (0.0-124.9)	51 6.1 (4.5-8.0)
Blood and blood-forming organs	0 0.0 (0.0-8.2)	2 11.8 (1.4-42.6)	1 13.3 (0.34-74.0)	3 12.3 (2.5-35.8)	7 2.1 (0.83-4.3)	4 7.0 (1.9-17.8)	11 2.7 (1.4-4.9)	10 2.7 (1.3-5.0)	0 0.0 (0.0-124.9)	24 2.9 (1.8-4.2)
Endocrine diseases	1 2.2 (0.06-12.4)	0 0.0 (0.0-21.8)	0 0.0 (0.0-49.0)	0 0.0 (0.0-15.1)	8 2.4 (1.0-4.7)	5 8.7 (2.8-20.3)	13 3.2 (1.7-5.5)	10 2.7 (1.3-5.0)	0 0.0 (0.0-124.9)	24 2.9 (1.8-4.2)
Mental and behavioral disorders	8 17.9 (7.7-35.1)	0 0.0 (0.0-21.8)	1 13.3 (0.34-74.0)	1 4.1 (0.10-22.8)	10 3.0 (1.4-5.4)	2 3.5 (0.42-12.6)	12 3.0 (1.5-5.2)	13 3.5 (1.9-6.0)	0 0.0 (0.0-124.9)	34 4.0 (2.8-5.6)
Nervous system	8 17.9 (7.7-35.1)	3 17.7 (3.7-51.7)	2 26.7 (3.2-96.0)	5 20.5 (6.6-47.7)	29 8.6 (5.7-12.3)	5 8.7 (2.8-20.3)	35 8.7 (6.1-12.1)	23 6.2 (4.0-9.4)	0 0.0 (0.0-124.9)	71 8.4 (6.6-10.6)
Eye	0 0.0 (0.0-8.2)	0 0.0 (0.0-21.8)	0 0.0 (0.0-49.0)	0 0.0 (0.0-15.1)	4 1.2 (0.32-3.0)	1 1.7 (0.04-9.7)	5 1.2 (0.40-2.9)	6 1.6 (0.60-3.5)	1 34.1 (0.86-188.3)	12 1.4 (0.74-2.5)
Ear	0 0.0 (0.0-8.2)	1 5.9 (0.15-32.9)	0 0.0 (0.0-49.0)	1 4.1 (0.10-22.8)	9 2.7 (1.2-5.1)	2 3.5 (0.42-12.6)	12 3.0 (1.5-5.2)	9 2.4 (1.1-4.6)	0 0.0 (0.0-124.9)	22 2.6 (1.6-4.0)
Cardiovascular system	13 29.0 (15.5-49.6)	6 35.4 (13.0-76.9)	1 13.3 (0.34-74.0)	7 28.6 (11.5-58.9)	82 24.3 (19.3-30.1)	26 45.2 (29.5-66.2)	114 28.4 (23.5-34.2)	102 27.7 (22.6-33.6)	0 0.0 (0.0-124.9)	236 28.0 (24.6-31.8)
Respiratory system	11 24.5 (12.3-43.9)	4 23.6 (6.4-60.4)	5 66.6 (21.7-154.8)	9 36.8 (16.9-69.8)	83 24.6 (19.6-30.4)	20 34.8 (21.2-53.6)	106 26.4 (21.7-32.0)	112 30.4 (25.0-36.5)	0 0.0 (0.0-124.9)	238 28.3 (24.8-32.1)

	DNG	*OAED*			*NAED*			*Ex-use*	*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*			
Digestive system	32 71.4 (48.9-100.6)	9 53.1 (24.3-100.6)	5 66.6 (21.7-154.8)	14 57.3 (31.4-95.9)	138 40.8 (34.3-48.2)	28 48.7 (32.4-70.3)	168 41.9 (35.8-48.7)	169 45.8 (39.2-53.3)	0 0.0 (0.0-124.9)	383 45.5 (41.1-50.3)
Skin	2 4.5 (0.54-16.1)	0 0.0 (0.0-21.8)	0 0.0 (0.0-49.0)	0 0.0 (0.0-15.1)	10 3.0 (1.4-5.4)	5 8.7 (2.8-20.3)	17 4.2 (2.5-6.8)	19 5.2 (3.1-8.0)	0 0.0 (0.0-124.9)	38 4.5 (3.2-6.2)
Musculoskeletal system and connective tissue	10 22.3 (10.7-41.0)	5 29.5 (9.6-68.8)	2 26.7 (3.2-96.0)	7 28.6 (11.5-58.9)	35 10.4 (7.2-14.4)	16 27.8 (15.9-45.1)	53 13.2 (9.9-17.3)	52 14.1 (10.5-18.5)	0 0.0 (0.0-124.9)	122 14.5 (12.0-17.3)
Genitourinary system	56 125.0 (94.5-162.0)	28 165.3 (110.1-238.1)	15 199.9 (112.3-327.6)	43 175.9 (127.6-236.3)	222 65.7 (57.3-74.9)	71 123.4 (96.5-155.4)	299 74.6 (66.4-83.5)	300 81.4 (72.4-91.1)	2 68.1 (8.3-243.9)	700 83.1 (77.1-89.5)
Pregnancy, delivery and puerperium	7 15.6 (6.3-32.2)	5 29.5 (9.6-68.8)	1 13.3 (0.34-74.0)	6 24.6 (9.0-53.4)	28 8.3 (5.5-12.0)	13 22.6 (12.0-38.6)	42 10.5 (7.6-14.2)	332 90.0 (80.6-100.2)	0 0.0 (0.0-124.9)	387 46.0 (41.5-50.8)
Malformations, deformations and chromosomal abnormalities	0 0.0 (0.0-8.2)	0 0.0 (0.0-21.8)	0 0.0 (0.0-49.0)	0 0.0 (0.0-15.1)	1 0.30 (0.007-1.6)	0 0.0 (0.0-6.4)	1 0.25 (0.006-1.4)	0 0.0 (0.0-1.0)	0 0.0 (0.0-124.9)	1 0.12 (0.003-0.66)
Injury, poisoning, accidents etc.	15 33.5 (18.7-55.1)	10 59.0 (28.3-108.3)	6 80.0 (29.4-173.3)	16 65.5 (37.5-106.1)	135 39.9 (33.5-47.2)	34 59.1 (41.0-82.5)	170 42.4 (36.3-49.3)	135 36.6 (30.7-43.3)	0 0.0 (0.0-124.9)	336 39.9 (35.8-44.4)

Note: **SAEs, which occurred within 3 months after stop of EMT, were attributed to the last EMT used by the women.
Therefore, pregnancy-related SAEs in XXX cohorts does not necessarily reflect unwanted pregnancies during EMT use.
Note: ***Incidence rate is shown per 10^4 women-years.

Table 62: Incidence rate of self-reported anemia, AT population, Germany

	DNG	OAED			NAED			Ex-use	Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED			
Number of women-years	820	49	0	49	1666	711	2408	2176	45	5498
Self-reported anemia	21	4		4	45	20	65	80	1	171
IR (95% CI)*	256.0 (159.1-388.7)	820.5 (228.1-1969.5)	0 0.0 (-)	820.5 (228.1-1969.5)	270.1 (197.6-359.7)	281.3 (172.7-431.2)	270.0 (209.0-342.8)	367.7 (292.6-455.6)	221.8 (5.6-1175.0)	311.1 (266.8-360.4)
Thereof										
Confirmed	1 12.2 (0.31-67.7)	0 0.0 (0.0-728.8)	0 0.0 (-)	0 0.0 (0.0-728.8)	4 24.0 (6.5-61.3)	1 14.1 (0.36-78.1)	5 20.8 (6.7-48.4)	4 18.4 (5.0-47.0)	0 0.0 (0.0-785.7)	10 18.2 (8.7-33.4)
Not confirmed	20 243.8 (149.5-374.0)	4 820.5 (228.1-1969.5)	0 0.0 (-)	4 820.5 (228.1-1969.5)	41 246.0 (177.1-332.3)	19 267.3 (161.7-414.2)	60 249.2 (190.7-319.6)	76 349.3 (276.2-435.3)	1 221.8 (5.6-1175.0)	161 292.9 (249.9-340.9)
Thereof										
Recurrent anemia	5 61.0 (19.8-141.7)	0 0.0 (0.0-728.8)	0 0.0 (-)	0 0.0 (0.0-728.8)	8 48.0 (20.7-94.4)	7 98.5 (39.7-201.8)	15 62.3 (34.9-102.5)	16 73.5 (42.1-119.2)	0 0.0 (0.0-785.7)	36 65.5 (45.9-90.5)
Potential anemia, no further clarification possible	3 36.6 (7.5-106.5)	0 0.0 (0.0-728.8)	0 0.0 (-)	0 0.0 (0.0-728.8)	3 18.0 (3.7-52.5)	2 28.1 (3.4-101.3)	5 20.8 (6.7-48.4)	2 9.2 (1.1-33.2)	0 0.0 (0.0-785.7)	10 18.2 (8.7-33.4)
Anemia caused by other reason** (other primary disease, surgery etc.)	5 61.0 (19.8-141.7)	1 205.1 (5.2-1090.7)	0 0.0 (-)	1 205.1 (5.2-1090.7)	6 36.0 (13.2-78.2)	1 14.1 (0.36-78.1)	7 29.1 (11.7-59.8)	33 151.7 (104.6-212.4)	0 0.0 (0.0-785.7)	46 83.7 (61.3-111.5)
Anemia not confirmed by diagnostic measures	1 12.2 (0.31-67.7)	0 0.0 (0.0-728.8)	0 0.0 (-)	0 0.0 (0.0-728.8)	5 30.0 (9.7-69.9)	2 28.1 (3.4-101.3)	7 29.1 (11.7-59.8)	1 4.6 (0.12-25.6)	0 0.0 (0.0-785.7)	9 16.4 (7.5-31.1)
Not treated by HCP	2 24.4 (3.0-87.8)	1 205.1 (5.2-1090.7)	0 0.0 (-)	1 205.1 (5.2-1090.7)	9 54.0 (24.7-102.3)	2 28.1 (3.4-101.3)	11 45.7 (22.8-81.6)	7 32.2 (12.9-66.2)	0 0.0 (0.0-785.7)	21 38.2 (23.7-58.3)
'No event'-before study, repetition	4 48.8 (13.3-124.4)	2 410.3 (50.1-1404.7)	0 0.0 (-)	2 410.3 (50.1-1404.7)	10 60.0 (28.8-110.1)	5 70.3 (22.9-163.4)	15 62.3 (34.9-102.5)	17 78.1 (45.6-124.8)	1 221.8 (5.6-1175.0)	39 70.9 (50.5-96.9)

Note: *Incidence rate is shown per 10^4 women-years

Table 63: Incidence rate of self-reported anemia, AT population, Poland

	DNG	OAED			NAED			Ex-use	Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED			
Number of women-years	449	9	36	45	783	186	989	2370	54	3908
Self-reported anemia	7		1	1	9		10	44	2	
IR** *(95% CI)	155.8 (62.9-318.5)	0 0.0 (0.0-3337.7)	276.5 (7.0-1446.6)	221.0 (5.6-1170.9)	114.9 (52.7-217.1)	1 53.8 (1.4-296.3)	101.1 (48.6-185.2)	185.6 (135.2-248.4)	370.9 (45.2-1276.6)	64 163.8 (126.4-208.7)
Thereof										
Confirmed	3 66.8 (13.8-193.9)	0 0.0 (0.0-3337.7)	0 0.0 (0.0-969.7)	0 0.0 (0.0-782.9)	0 0.0 (0.0-47.0)	1 53.8 (1.4-296.3)	1 10.1 (0.26-56.2)	13 54.8 (29.2-93.6)	0 0.0 (0.0-661.3)	17 43.5 (25.4-69.6)
Not confirmed	4 89.1 (24.3-226.4)	0 0.0 (0.0-3337.7)	1 276.5 (7.0-1446.6)	1 221.0 (5.6-1170.9)	9 114.9 (52.7-217.1)	0 0.0 (0.0-196.6)	9 91.0 (41.7-172.1)	31 130.8 (89.0-185.1)	2 370.9 (45.2-1276.6)	47 120.3 (88.5-159.6)
Thereof										
Recurrent anemia	3 66.8 (13.8-193.9)	0 0.0 (0.0-3337.7)	1 276.5 (7.0-1446.6)	1 221.0 (5.6-1170.9)	4 51.1 (13.9-130.3)	0 0.0 (0.0-196.6)	4 40.4 (11.0-103.2)	13 54.8 (29.2-93.6)	0 0.0 (0.0-661.3)	21 53.7 (33.3-82.0)
Potential anemia, no further clarification possible	1 22.3 (0.56-123.4)	0 0.0 (0.0-3337.7)	0 0.0 (0.0-969.7)	0 0.0 (0.0-782.9)	3 38.3 (7.9-111.6)	0 0.0 (0.0-196.6)	3 30.3 (6.3-88.4)	6 25.3 (9.3-55.0)	2 370.9 (45.2-1276.6)	12 30.7 (15.9-53.6)
Anemia caused by other reason** (other primary disease, surgery etc.)	0 0.0 (0.0-81.8)	0 0.0 (0.0-3337.7)	0 0.0 (0.0-969.7)	0 0.0 (0.0-782.9)	0 0.0 (0.0-47.0)	0 0.0 (0.0-196.6)	0 0.0 (0.0-37.2)	11 46.4 (23.2-82.9)	0 0.0 (0.0-661.3)	11 28.2 (14.1-50.3)
Anemia not confirmed by diagnostic measures	0 0.0 (0.0-81.8)	0 0.0 (0.0-3337.7)	0 0.0 (0.0-969.7)	0 0.0 (0.0-782.9)	0 0.0 (0.0-47.0)	0 0.0 (0.0-196.6)	0 0.0 (0.0-37.2)	0 0.0 (0.0-15.6)	0 0.0 (0.0-661.3)	0 0.0 (0.0-9.4)
Not treated by HCP	0 0.0 (0.0-81.8)	0 0.0 (0.0-3337.7)	0 0.0 (0.0-969.7)	0 0.0 (0.0-782.9)	2 25.5 (3.1-92.0)	0 0.0 (0.0-196.6)	2 20.2 (2.5-72.9)	1 4.2 (0.11-23.5)	0 0.0 (0.0-661.3)	3 7.7 (1.6-22.4)
'No event'-before study, repetition	0 0.0 (0.0-81.8)	0 0.0 (0.0-3337.7)	0 0.0 (0.0-969.7)	0 0.0 (0.0-782.9)	0 0.0 (0.0-47.0)	0 0.0 (0.0-196.6)	0 0.0 (0.0-37.2)	0 0.0 (0.0-15.6)	0 0.0 (0.0-661.3)	0 0.0 (0.0-9.4)

Note: *Incidence rate is shown per 10^4 women-years.

Table 64: Incidence rate of self-reported anemia, AT population, Hungary

	DNG	*OAED*			*NAED*			*Ex-use*	*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*			
Number of women-years	1553	292	1	294	17004	659	17717	12907	80	32550
Self-reported anemia	21	5		5						
IR (95% CI)*	135.3 (83.9-206.0)	171.1 (55.8-394.8)	0 0.0 (0.0-9260.2)	170.3 (55.5-392.9)	64 37.6 (29.0-48.0)	9 136.7 (62.7-257.9)	75 42.3 (33.3-53.0)	82 63.5 (50.6-78.8)	0 0.0 (0.0-451.6)	183 56.2 (48.4-65.0)
Thereof										
Confirmed	5 32.2 (10.5-75.0)	1 34.2 (0.87-189.2)	0 0.0 (0.0-9260.2)	1 34.1 (0.86-188.3)	5 2.9 (0.95-6.9)	1 15.2 (0.38-84.3)	6 3.4 (1.2-7.4)	8 6.2 (2.7-12.2)	0 0.0 (0.0-451.6)	20 6.1 (3.8-9.5)
Not confirmed	16 103.1 (59.0-166.8)	4 136.9 (37.4-346.8)	0 0.0 (0.0-9260.2)	4 136.2 (37.2-345.2)	59 34.7 (26.4-44.7)	8 121.5 (52.6-238.0)	69 38.9 (30.3-49.3)	74 57.3 (45.0-71.9)	0 0.0 (0.0-451.6)	163 50.1 (42.7-58.4)
Thereof										
Recurrent anemia	6 38.6 (14.2-83.9)	0 0.0 (0.0-125.5)	0 0.0 (0.0-9260.2)	0 0.0 (0.0-124.9)	14 8.2 (4.5-13.8)	3 45.6 (9.4-132.6)	17 9.6 (5.6-15.4)	10 7.7 (3.7-14.2)	0 0.0 (0.0-451.6)	33 10.1 (7.0-14.2)
Potential anemia, no further clarification possible	1 6.4 (0.16-35.8)	2 68.5 (8.3-245.1)	0 0.0 (0.0-9260.2)	2 68.1 (8.3-243.9)	10 5.9 (2.8-10.8)	2 30.4 (3.7-109.3)	12 6.8 (3.5-11.8)	9 7.0 (3.2-13.2)	0 0.0 (0.0-451.6)	24 7.4 (4.7-11.0)
Anemia caused by other reason** (other primary disease, surgery etc.)	3 19.3 (4.0-56.4)	0 0.0 (0.0-125.5)	0 0.0 (0.0-9260.2)	0 0.0 (0.0-124.9)	6 3.5 (1.3-7.7)	1 15.2 (0.38-84.3)	8 4.5 (1.9-8.9)	29 22.5 (15.1-32.3)	0 0.0 (0.0-451.6)	40 12.3 (8.8-16.7)
Anemia not confirmed by diagnostic measures	0 0.0 (0.0-23.7)	0 0.0 (0.0-125.5)	0 0.0 (0.0-9260.2)	0 0.0 (0.0-124.9)	5 2.9 (0.95-6.9)	0 0.0 (0.0-55.9)	5 2.8 (0.92-6.6)	8 6.2 (2.7-12.2)	0 0.0 (0.0-451.6)	13 4.0 (2.1-6.8)
Not treated by HCP	6 38.6 (14.2-83.9)	1 34.2 (0.87-189.2)	0 0.0 (0.0-9260.2)	1 34.1 (0.86-188.3)	20 11.8 (7.2-18.2)	1 15.2 (0.38-84.3)	22 12.4 (7.8-18.8)	17 13.2 (7.7-21.1)	0 0.0 (0.0-451.6)	46 14.1 (10.3-18.8)
'No event'-before study, repetition	0 0.0 (0.0-23.7)	1 34.2 (0.87-189.2)	0 0.0 (0.0-9260.2)	1 34.1 (0.86-188.3)	4 2.4 (0.64-6.0)	1 15.2 (0.38-84.3)	5 2.8 (0.92-6.6)	1 0.77 (0.02-4.3)	0 0.0 (0.0-451.6)	7 2.2 (0.86-4.4)

Note: *Incidence rate is shown per 10^4 women-years.

Table 65: Incidence rate of self-reported anemia, AT population, Switzerland

	DNG	*OAED*			*NAED*			*Ex-use*	*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*			
Number of women-years	49	1	0	1	11	6	18	13	4	84
Self-reported anemia	4				2		2	2		8
IR (95% CI)*	813.6 (226.1-1953.9)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	1764.7 (221.3-5060.7)	0 0.0 (0.0-4502.0)	1121.5 (138.8-3498.9)	1548.4 (193.3-4568.1)	0 0.0 (0.0-6514.5)	952.4 (420.2-1790.6)
Thereof										
Confirmed	1				0					1
	203.4 (5.1-1081.9)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	0.0 (0.0-2778.3)	0 0.0 (0.0-4502.0)	0 0.0 (0.0-1868.6)	0 0.0 (0.0-2484.3)	0 0.0 (0.0-6514.5)	119.0 (3.0-645.5)
Not confirmed	3				2		2	2		7
	610.2 (127.6-1681.2)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	1764.7 (221.3-5060.7)	0 0.0 (0.0-4502.0)	1121.5 (138.8-3498.9)	1548.4 (193.3-4568.1)	0 0.0 (0.0-6514.5)	833.3 (341.6-1641.9)
Thereof										
Recurrent anemia					0					
	0 0.0 (0.0-722.8)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	0.0 (0.0-2778.3)	0 0.0 (0.0-4502.0)	0 0.0 (0.0-1868.6)	0 0.0 (0.0-2484.3)	0 0.0 (0.0-6514.5)	0 0.0 (0.0-429.6)
Potential anemia, no further clarification possible	2				2		2	2		6
	406.8 (49.6-1393.4)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	1764.7 (221.3-5060.7)	0 0.0 (0.0-4502.0)	1121.5 (138.8-3498.9)	1548.4 (193.3-4568.1)	0 0.0 (0.0-6514.5)	714.3 (266.6-1490.1)
Anemia caused by other reason** (other primary disease, surgery etc.)	0 0.0 (0.0-722.8)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	0 0.0 (0.0-2778.3)	0 0.0 (0.0-4502.0)	0 0.0 (0.0-1868.6)	0 0.0 (0.0-2484.3)	0 0.0 (0.0-6514.5)	0 0.0 (0.0-429.6)
Anemia not confirmed by diagnostic measures	0 0.0 (0.0-722.8)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	0 0.0 (0.0-2778.3)	0 0.0 (0.0-4502.0)	0 0.0 (0.0-1868.6)	0 0.0 (0.0-2484.3)	0 0.0 (0.0-6514.5)	0 0.0 (0.0-429.6)
Not treated by HCP	0 0.0 (0.0-722.8)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	0 0.0 (0.0-2778.3)	0 0.0 (0.0-4502.0)	0 0.0 (0.0-1868.6)	0 0.0 (0.0-2484.3)	0 0.0 (0.0-6514.5)	0 0.0 (0.0-429.6)
'No event'-before study, repetition	1 203.4 (5.1-1081.9)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	0 0.0 (0.0-2778.3)	0 0.0 (0.0-4502.0)	0 0.0 (0.0-1868.6)	0 0.0 (0.0-2484.3)	0 0.0 (0.0-6514.5)	1 119.0 (3.0-645.5)

Note: *Incidence rate is shown per 10^4 women-years.

Table 66: Incidence rate of self-reported anemia, AT population, Russia

	DNG	*OAED*			*NAED*			*Ex-use*	*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*			
Number of women-years	1194	1143	211	1354	13027	2811	16217	14972	46	33782
Self-reported anemia	9	13	3	16	149	29	181	182	1	389
IR* *(95% CI)*	75.4 (34.5-142.7)	113.7 (60.7-193.7)	142.4 (29.5-410.5)	118.2 (67.7-191.2)	114.4 (96.8-134.2)	103.2 (69.2-147.8)	111.6 (96.0-129.0)	121.6 (104.6-140.4)	218.6 (5.5-1158.7)	115.1 (104.0-127.1)
Thereof										
Confirmed	3	2	1	3	57	11	70	44	0	120
	25.1 (5.2-73.3)	17.5 (2.1-63.1)	47.5 (1.2-261.6)	22.2 (4.6-64.6)	43.8 (33.2-56.7)	39.1 (19.6-69.9)	43.2 (33.7-54.5)	29.4 (21.4-39.4)	0.0 (0.0-774.7)	35.5 (29.5-42.5)
Not confirmed	6	11	2	13	92	18	111	138	1	269
	50.3 (18.5-109.1)	96.2 (48.1-171.5)	94.9 (11.5-338.7)	96.0 (51.2-163.7)	70.6 (57.0-86.5)	64.0 (38.0-101.0)	68.4 (56.3-82.4)	92.2 (77.5-108.8)	218.6 (5.5-1158.7)	79.6 (70.4-89.7)
Thereof										
Recurrent anemia	3	6	0	6	49	7	56	27	0	92
	25.1 (5.2-73.3)	52.5 (19.3-113.9)	0.0 (0.0-173.6)	44.3 (16.3-96.2)	37.6 (27.8-49.7)	24.9 (10.0-51.2)	34.5 (26.1-44.8)	18.0 (11.9-26.2)	0.0 (0.0-774.7)	27.2 (22.0-33.4)
Potential anemia, no further clarification possible	1	1	1	2	8	1	9	12	1	25
	8.4 (0.21-46.6)	8.7 (0.22-48.6)	47.5 (1.2-261.6)	14.8 (1.8-53.3)	6.1 (2.7-12.1)	3.6 (0.09-19.8)	5.5 (2.5-10.5)	8.0 (4.1-14.0)	218.6 (5.5-1158.7)	7.4 (4.8-10.9)
Anemia caused by other reason** (other primary disease, surgery etc.)	1	1	0	1	11	3	14	62	0	78
	8.4 (0.21-46.6)	8.7 (0.22-48.6)	0.0 (0.0-173.6)	7.4 (0.19-41.1)	8.4 (4.2-15.1)	10.7 (2.2-31.2)	8.6 (4.7-14.5)	41.4 (31.8-53.1)	0.0 (0.0-774.7)	23.1 (18.3-28.8)
Anemia not confirmed by diagnostic measures	0	0	0	0	2	0	2	5	0	7
	0.0 (0.0-30.9)	0.0 (0.0-32.2)	0.0 (0.0-173.6)	0.0 (0.0-27.2)	1.5 (0.19-5.5)	0.0 (0.0-13.1)	1.2 (0.15-4.5)	3.3 (1.1-7.8)	0.0 (0.0-774.7)	2.1 (0.83-4.3)
Not treated by HCP	1	2	1	3	19	4	24	26	0	54
	8.4 (0.21-46.6)	17.5 (2.1-63.1)	47.5 (1.2-261.6)	22.2 (4.6-64.6)	14.6 (8.8-22.8)	14.2 (3.9-36.4)	14.8 (9.5-22.0)	17.4 (11.3-25.4)	0.0 (0.0-774.7)	16.0 (12.0-20.9)
'No event'-before study, repetition	0	1	0	1	3	3	6	6	0	13
	0.0 (0.0-30.9)	8.7 (0.22-48.6)	0.0 (0.0-173.6)	7.4 (0.19-41.1)	2.3 (0.47-6.7)	10.7 (2.2-31.2)	3.7 (1.4-8.1)	4.0 (1.5-8.7)	0.0 (0.0-774.7)	3.8 (2.0-6.6)

Note: *Incidence rate is shown per 10^4 women-years.

Table 67: Incidence rate of self-reported anemia, AT population, Ukraine

	DNG	*OAED*			*NAED*			*Ex-use*	*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*			
Number of women-years	417	200	502	702	1314	1380	2741	4439	66	8365
Self-reported anemia	7	4	8	12	28	27	56	68		143
IR (95% CI)*	167.9 (67.8-342.8)	199.9 (54.7-503.9)	159.4 (69.0-311.6)	170.9 (88.6-296.7)	213.1 (142.0-306.5)	195.6 (129.3-283.3)	204.3 (154.7-264.5)	153.2 (119.1-193.8)	0 0.0 (0.0-547.6)	170.9 (144.3-201.1)
Thereof										
Confirmed	2 48.0 (5.8-172.2)	3 149.9 (31.0-431.9)	5 99.6 (32.4-230.9)	8 113.9 (49.3-223.3)	6 45.7 (16.8-99.1)	4 29.0 (7.9-74.0)	10 36.5 (17.5-67.0)	9 20.3 (9.3-38.4)	0 0.0 (0.0-547.6)	29 34.7 (23.2-49.8)
Not confirmed	5 119.9 (39.0-277.6)	1 50.0 (1.3-275.3)	3 59.8 (12.3-173.6)	4 57.0 (15.5-145.2)	22 167.4 (105.2-252.4)	23 166.6 (105.9-249.0)	46 167.8 (123.1-223.2)	59 132.9 (101.3-171.1)	0 0.0 (0.0-547.6)	114 136.3 (112.5-163.5)
Thereof										
Recurrent anemia	3 71.9 (14.9-208.8)	1 50.0 (1.3-275.3)	0 0.0 (0.0-73.2)	1 14.2 (0.36-79.1)	10 76.1 (36.5-139.5)	14 101.4 (55.6-169.6)	24 87.6 (56.2-130.0)	17 38.3 (22.3-61.2)	0 0.0 (0.0-547.6)	45 53.8 (39.3-71.9)
Potential anemia, no further clarification possible	0 0.0 (0.0-88.1)	0 0.0 (0.0-182.7)	0 0.0 (0.0-73.2)	0 0.0 (0.0-52.4)	1 7.6 (0.19-42.3)	2 14.5 (1.8-52.2)	3 10.9 (2.3-32.0)	5 11.3 (3.7-26.3)	0 0.0 (0.0-547.6)	8 9.6 (4.1-18.8)
Anemia caused by other reason** (other primary disease, surgery etc.)	0 0.0 (0.0-88.1)	0 0.0 (0.0-182.7)	0 0.0 (0.0-73.2)	0 0.0 (0.0-52.4)	4 30.4 (8.3-77.7)	2 14.5 (1.8-52.2)	7 25.5 (10.3-52.5)	19 42.8 (25.8-66.8)	0 0.0 (0.0-547.6)	26 31.1 (20.3-45.5)
Anemia not confirmed by diagnostic measures	0 0.0 (0.0-88.1)	0 0.0 (0.0-182.7)	1 19.9 (0.50-110.5)	1 14.2 (0.36-79.1)	1 7.6 (0.19-42.3)	0 0.0 (0.0-26.7)	1 3.6 (0.09-20.3)	0 0.0 (0.0-8.3)	0 0.0 (0.0-547.6)	2 2.4 (0.29-8.6)
Not treated by HCP	1 24.0 (0.61-132.9)	0 0.0 (0.0-182.7)	2 39.8 (4.8-143.2)	2 28.5 (3.5-102.5)	5 38.0 (12.4-88.6)	1 7.2 (0.18-40.3)	6 21.9 (8.0-47.6)	14 31.5 (17.3-52.9)	0 0.0 (0.0-547.6)	23 27.5 (17.4-41.2)
'No event'-before study, repetition	1 24.0 (0.61-132.9)	0 0.0 (0.0-182.7)	0 0.0 (0.0-73.2)	0 0.0 (0.0-52.4)	1 7.6 (0.19-42.3)	4 29.0 (7.9-74.0)	5 18.2 (5.9-42.5)	4 9.0 (2.5-23.1)	0 0.0 (0.0-547.6)	10 12.0 (5.7-22.0)

Note: *Incidence rate is shown per 10^4 women-years.

Table 68: Incidence rate of self-reported depression, AT population, Germany

	DNG	*OAED*			*NAED*			*Ex-use*	*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*			
Number of women-years	820	49	0	49	1666	711	2408	2176	45	5498
Self-reported depression	95	14		14	107	59	166	102	1	
***IR**[*] (95% CI)*	1158.1 (947.1-1397.1)	2871.8 (1667.5-4346.0)	0 0.0 (-)	2871.8 (1667.5-4346.0)	642.1 (529.2-770.7)	829.9 (637.8-1057.5)	689.4 (591.5-798.1)	468.8 (383.9-566.3)	221.8 (5.6-1175.0)	378 687.6 (622.1-757.7)
Thereof										
Confirmed	7	0	0	0	8	6	14	13	0	34
	85.3 (34.4-175.0)	0.0 (0.0-728.8)	0.0 (-)	0.0 (0.0-728.8)	48.0 (20.7-94.4)	84.4 (31.0-182.8)	58.1 (31.8-97.4)	59.8 (31.9-102.0)	0.0 (0.0-785.7)	61.8 (42.9-86.3)
Not confirmed	88	14		14	99	53	152	89	1	
	1072.7 (869.3-1304.9)	2871.8 (1667.5-4346.0)	0 0.0 (-)	2871.8 (1667.5-4346.0)	594.1 (485.5-718.6)	745.5 (563.4-963.8)	631.3 (537.4-735.9)	409.1 (329.8-501.0)	221.8 (5.6-1175.0)	344 625.7 (563.1-693.0)
Thereof										
Recurrent depression					15					
	19 231.6 (140.0-359.3)	0 0.0 (0.0-728.8)	0 0.0 (-)	0 0.0 (0.0-728.8)	90.0 (50.5-148.0)	5 70.3 (22.9-163.4)	20 83.1 (50.8-128.0)	15 68.9 (38.6-113.5)	0 0.0 (0.0-785.7)	54 98.2 (73.9-128.0)
Potential depression, no further clarification possible	4 48.8 (13.3-124.4)	2 410.3 (50.1-1404.7)	0 0.0 (-)	2 410.3 (50.1-1404.7)	8 48.0 (20.7-94.4)	10 140.7 (67.7-257.2)	18 74.8 (44.4-117.9)	11 50.6 (25.3-90.3)	1 221.8 (5.6-1175.0)	36 65.5 (45.9-90.5)
Depression treated by GP	17 207.2 (121.2-329.7)	2 410.3 (50.1-1404.7)	0 0.0 (-)	2 410.3 (50.1-1404.7)	20 120.0 (73.5-184.8)	9 126.6 (58.0-239.0)	29 120.4 (80.8-172.5)	8 36.8 (15.9-72.3)	0 0.0 (0.0-785.7)	56 101.9 (77.0-132.1)
Depressive disorders treated by psychologist	10 121.9 (58.6-223.0)	3 615.4 (128.8-1694.7)	0 0.0 (-)	3 615.4 (128.8-1694.7)	15 90.0 (50.5-148.0)	9 126.6 (58.0-239.0)	24 99.7 (64.0-148.0)	4 18.4 (5.0-47.0)	0 0.0 (0.0-785.7)	41 74.6 (53.6-101.0)
Other psychiatric disorders[**]	1 12.2 (0.31-67.7)	0 0.0 (0.0-728.8)	0 0.0 (-)	0 0.0 (0.0-728.8)	7 42.0 (16.9-86.4)	1 14.1 (0.36-78.1)	8 33.2 (14.4-65.4)	4 18.4 (5.0-47.0)	0 0.0 (0.0-785.7)	13 23.6 (12.6-40.4)
Other psychic problems[***]	5 61.0 (19.8-141.7)	2 410.3 (50.1-1404.7)	0 0.0 (-)	2 410.3 (50.1-1404.7)	7 42.0 (16.9-86.4)	5 70.3 (22.9-163.4)	12 49.8 (25.8-86.9)	7 32.2 (12.9-66.2)	0 0.0 (0.0-785.7)	26 47.3 (30.9-69.2)
'No event'-before study, repetition	32 390.1 (268.3-546.2)	5 1025.6 (341.5-2233.4)	0 0.0 (-)	5 1025.6 (341.5-2233.4)	27 162.0 (107.0-234.9)	14 196.9 (108.1-328.2)	41 170.3 (122.5-230.3)	40 183.9 (131.7-249.5)	0 0.0 (0.0-785.7)	118 214.6 (178.0-256.5)

	DNG	OAED			NAED			Ex-use	Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED			

Note: *Incidence rate is shown per 10^4 women-years. Note: **Includes e.g. schizophrenia, bipolar, anxiety, eating disorders. Note: ***Includes e.g. mood changes, psychosomatic disorders, no HCP visited.

Table 69: Incidence rate of self-reported depression, AT population, Poland

	DNG	*OAED*			*NAED*			*Ex-use*	*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*			
Number of women-years	449	9	36	45	783	186	989	2370	54	3908
Self-reported depression			5	5	5		10	25	1	
IR (95% CI)*	13 289.4 (155.0-489.8)	0 0.0 (0.0-3337.7)	1382.5 (464.5-2937.5)	1105.0 (368.7-2393.1)	63.9 (20.8-148.4)	4 215.3 (59.0-542.2)	101.1 (48.6-185.2)	105.5 (68.4-155.3)	185.5 (4.7-990.6)	54 138.2 (104.0-179.9)
Thereof										
Confirmed								9		
	2 44.5 (5.4-159.9)	0 0.0 (0.0-3337.7)	0 0.0 (0.0-969.7)	0 0.0 (0.0-782.9)	0 0.0 (0.0-47.0)	1 53.8 (1.4-296.3)	1 10.1 (0.26-56.2)	38.0 (17.4-72.0)	0 0.0 (0.0-661.3)	12 30.7 (15.9-53.6)
Not confirmed			5	5	5		9	16	1	
	11 244.9 (122.9-434.0)	0 0.0 (0.0-3337.7)	1382.5 (464.5-2937.5)	1105.0 (368.7-2393.1)	63.9 (20.8-148.4)	3 161.5 (33.4-464.7)	91.0 (41.7-172.1)	67.5 (38.6-109.4)	185.5 (4.7-990.6)	42 107.5 (77.6-145.0)
Thereof										
Recurrent depression					1					
	2 44.5 (5.4-159.9)	0 0.0 (0.0-3337.7)	0 0.0 (0.0-969.7)	0 0.0 (0.0-782.9)	12.8 (0.32-71.0)	0 0.0 (0.0-196.6)	1 10.1 (0.26-56.2)	3 12.7 (2.6-36.9)	0 0.0 (0.0-661.3)	6 15.4 (5.6-33.4)
Potential depression, no further clarification possible	1	0	1	1	1	0	2	1	0	5
	22.3 (0.56-123.4)	0.0 (0.0-3337.7)	276.5 (7.0-1446.6)	221.0 (5.6-1170.9)	12.8 (0.32-71.0)	0.0 (0.0-196.6)	20.2 (2.5-72.9)	4.2 (0.11-23.5)	0.0 (0.0-661.3)	12.8 (4.2-29.8)
Depression treated by GP	3	0	1	1	0	0	0	3	0	7
	66.8 (13.8-193.9)	0.0 (0.0-3337.7)	276.5 (7.0-1446.6)	221.0 (5.6-1170.9)	0.0 (0.0-47.0)	0.0 (0.0-196.6)	0.0 (0.0-37.2)	12.7 (2.6-36.9)	0.0 (0.0-661.3)	17.9 (7.2-36.9)
Depressive disorders treated by psychologist	1	0	1	1	0	0	0	1	0	3
	22.3 (0.56-123.4)	0.0 (0.0-3337.7)	276.5 (7.0-1446.6)	221.0 (5.6-1170.9)	0.0 (0.0-47.0)	0.0 (0.0-196.6)	0.0 (0.0-37.2)	4.2 (0.11-23.5)	0.0 (0.0-661.3)	7.7 (1.6-22.4)
Other psychiatric disorders**									1	
	1 22.3 (0.56-123.4)	0 0.0 (0.0-3337.7)	0 0.0 (0.0-969.7)	0 0.0 (0.0-782.9)	0 0.0 (0.0-47.0)	2 107.7 (13.1-383.5)	2 20.2 (2.5-72.9)	4 16.9 (4.6-43.2)	185.5 (4.7-990.6)	8 20.5 (8.8-40.3)
Other psychic problems***					1					
	1 22.3 (0.56-123.4)	0 0.0 (0.0-3337.7)	0 0.0 (0.0-969.7)	0 0.0 (0.0-782.9)	12.8 (0.32-71.0)	0 0.0 (0.0-196.6)	1 10.1 (0.26-56.2)	3 12.7 (2.6-36.9)	0 0.0 (0.0-661.3)	5 12.8 (4.2-29.8)

	DNG	OAED			NAED			Ex-use	Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED			
'No event'-before study, repetition	2 44.5 (5.4-159.9)	0 0.0 (0.0-3337.7)	2 553.0 (67.7-1858.4)	2 442.0 (54.0-1507.0)	2 25.5 (3.1-92.0)	1 53.8 (1.4-296.3)	3 30.3 (6.3-88.4)	1 4.2 (0.11-23.5)	0 0.0 (0.0-661.3)	8 20.5 (8.8-40.3)

Note: *Incidence rate is shown per 10^4 women-years. Note: **Includes e.g. schizophrenia, bipolar, anxiety, eating disorders. Note: ***Includes e.g. mood changes, psychosomatic disorders, no HCP visited.

Table 70: Incidence rate of self-reported depression, AT population, Hungary

	DNG	OAED			NAED			Ex-use	Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED			
Number of women-years	1553	292	1	294	17004	659	17717	12907	80	32550
Self-reported depression					134			87		
IR* (95% CI)	31 199.7 (136.1-282.2)	4 136.9 (37.4-346.8)	0 0.0 (0.0-9260.2)	4 136.2 (37.2-345.2)	78.8 (66.1-93.3)	4 60.7 (16.6-154.8)	138 77.9 (65.5-92.0)	67.4 (54.0-83.1)	0 0.0 (0.0-451.6)	260 79.9 (70.5-90.2)
Thereof										
Confirmed					40			22		
	6 38.6 (14.2-83.9)	1 34.2 (0.87-189.2)	0 0.0 (0.0-9260.2)	1 34.1 (0.86-188.3)	23.5 (16.8-32.0)	1 15.2 (0.38-84.3)	41 23.1 (16.6-31.4)	17.0 (10.7-25.8)	0 0.0 (0.0-451.6)	70 21.5 (16.8-27.2)
Not confirmed					94			65		
	25 161.0 (104.5-236.8)	3 102.7 (21.2-297.1)	0 0.0 (0.0-9260.2)	3 102.2 (21.1-295.7)	55.3 (44.7-67.6)	3 45.6 (9.4-132.6)	97 54.7 (44.4-66.7)	50.4 (38.9-64.1)	0 0.0 (0.0-451.6)	190 58.4 (50.4-67.3)
Thereof										
Recurrent depression					21					
	9 58.0 (26.5-109.8)	1 34.2 (0.87-189.2)	0 0.0 (0.0-9260.2)	1 34.1 (0.86-188.3)	12.4 (7.6-18.9)	1 15.2 (0.38-84.3)	22 12.4 (7.8-18.8)	13 10.1 (5.4-17.2)	0 0.0 (0.0-451.6)	45 13.8 (10.1-18.5)
Potential depression, no further clarification possible	3 19.3 (4.0-56.4)	1 34.2 (0.87-189.2)	0 0.0 (0.0-9260.2)	1 34.1 (0.86-188.3)	14 8.2 (4.5-13.8)	0 0.0 (0.0-55.9)	14 7.9 (4.3-13.3)	21 16.3 (10.1-24.9)	0 0.0 (0.0-451.6)	39 12.0 (8.5-16.4)
Depression treated by GP	1 6.4 (0.16-35.8)	0 0.0 (0.0-125.5)	0 0.0 (0.0-9260.2)	0 0.0 (0.0-124.9)	3 1.8 (0.36-5.2)	0 0.0 (0.0-55.9)	3 1.7 (0.35-4.9)	3 2.3 (0.48-6.8)	0 0.0 (0.0-451.6)	7 2.2 (0.86-4.4)
Depressive disorders treated by psychologist	0 0.0 (0.0-23.7)	0 0.0 (0.0-125.5)	0 0.0 (0.0-9260.2)	0 0.0 (0.0-124.9)	10 5.9 (2.8-10.8)	0 0.0 (0.0-55.9)	10 5.6 (2.7-10.4)	2 1.5 (0.19-5.6)	0 0.0 (0.0-451.6)	12 3.7 (1.9-6.4)

	DNG	OAED				NAED		Ex-use	Allocation unknown	Total
		GnRH-a	Danazol	All OAED	CHC	Other progestins	All NAED			
Other psychiatric disorders**	1 6.4 (0.16-35.8)	0 0.0 (0.0-125.5)	0 0.0 (0.0-9260.2)	0 0.0 (0.0-124.9)	23 13.5 (8.6-20.3)	1 15.2 (0.38-84.3)	24 13.5 (8.7-20.1)	6 4.6 (1.7-10.1)	0 0.0 (0.0-451.6)	31 9.5 (6.5-13.5)
Other psychic problems***	6 38.6 (14.2-83.9)	1 34.2 (0.87-189.2)	0 0.0 (0.0-9260.2)	1 34.1 (0.86-188.3)	15 8.8 (4.9-14.5)	1 15.2 (0.38-84.3)	16 9.0 (5.2-14.7)	13 10.1 (5.4-17.2)	0 0.0 (0.0-451.6)	36 11.1 (7.7-15.3)
'No event'-before study, repetition	5 32.2 (10.5-75.0)	0 0.0 (0.0-125.5)	0 0.0 (0.0-9260.2)	0 0.0 (0.0-124.9)	8 4.7 (2.0-9.3)	0 0.0 (0.0-55.9)	8 4.5 (1.9-8.9)	7 5.4 (2.2-11.2)	0 0.0 (0.0-451.6)	20 6.1 (3.8-9.5)

Note: *Incidence rate is shown per 10^4 women-years. Note: **Includes e.g. schizophrenia, bipolar, anxiety, eating disorders. Note: ***Includes e.g. mood changes, psychosomatic disorders, no HCP visited.

Table 71: Incidence rate of self-reported depression, AT population, Switzerland

	DNG	*OAED*			*NAED*			*Ex-use*	*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*			
Number of women-years	49	1	0	1	11	6	18	13	4	84
Self-reported depression	5				3	1	4			9
IR (95% CI)*	1016.9 (338.5-2215.8)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	2647.1 (583.2-5966.1)	1621.6 (41.0-6300.0)	2243.0 (647.3-4800.0)	0 0.0 (0.0-2484.3)	0 0.0 (0.0-6514.5)	1071.4 (501.8-1936.7)
Thereof										
Confirmed	0 0.0 (0.0-722.8)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	0 0.0 (0.0-2778.3)	0 0.0 (0.0-4502.0)	0 0.0 (0.0-1868.6)	0 0.0 (0.0-2484.3)	0 0.0 (0.0-6514.5)	0 0.0 (0.0-429.6)
Not confirmed	5 1016.9 (338.5-2215.8)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	3 2647.1 (583.2-5966.1)	1 1621.6 (41.0-6300.0)	4 2243.0 (647.3-4800.0)	0 0.0 (0.0-2484.3)	0 0.0 (0.0-6514.5)	9 1071.4 (501.8-1936.7)
Thereof										
Recurrent depression	1 203.4 (5.1-1081.9)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	0 0.0 (0.0-2778.3)	0 0.0 (0.0-4502.0)	0 0.0 (0.0-1868.6)	0 0.0 (0.0-2484.3)	0 0.0 (0.0-6514.5)	1 119.0 (3.0-645.5)
Potential depression, no further clarification possible	2 406.8 (49.6-1393.4)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	1 882.4 (22.3-4030.2)	1 1621.6 (41.0-6300.0)	2 1121.5 (138.8-3498.9)	0 0.0 (0.0-2484.3)	0 0.0 (0.0-6514.5)	4 476.2 (131.3-1174.6)
Depression treated by GP	0 0.0 (0.0-722.8)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	0 0.0 (0.0-2778.3)	0 0.0 (0.0-4502.0)	0 0.0 (0.0-1868.6)	0 0.0 (0.0-2484.3)	0 0.0 (0.0-6514.5)	0 0.0 (0.0-429.6)
Depressive disorders treated by psychologist	0 0.0 (0.0-722.8)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	0 0.0 (0.0-2778.3)	0 0.0 (0.0-4502.0)	0 0.0 (0.0-1868.6)	0 0.0 (0.0-2484.3)	0 0.0 (0.0-6514.5)	0 0.0 (0.0-429.6)
Other psychiatric disorders**	0 0.0 (0.0-722.8)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	0 0.0 (0.0-2778.3)	0 0.0 (0.0-4502.0)	0 0.0 (0.0-1868.6)	0 0.0 (0.0-2484.3)	0 0.0 (0.0-6514.5)	0 0.0 (0.0-429.6)
Other psychic problems***	0 0.0 (0.0-722.8)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	1 882.4 (22.3-4030.2)	0 0.0 (0.0-4502.0)	1 560.7 (14.2-2751.7)	0 0.0 (0.0-2484.3)	0 0.0 (0.0-6514.5)	1 119.0 (3.0-645.5)
'No event'-before study, repetition	2 406.8 (49.6-1393.4)	0 0.0 (0.0-9982.1)	0 0.0 (-)	0 0.0 (0.0-9982.1)	1 882.4 (22.3-4030.2)	0 0.0 (0.0-4502.0)	1 560.7 (14.2-2751.7)	0 0.0 (0.0-2484.3)	0 0.0 (0.0-6514.5)	3 357.1 (74.3-1008.4)

Note: *Incidence rate is shown per 10^4 women-years. Note: **Includes e.g. schizophrenia, bipolar, anxiety, eating disorders. Note: ***Includes e.g. mood changes, psychosomatic disorders, no HCP visited.

Table 72: Incidence rate of self-reported depression, AT population, Russia

	DNG	*OAED*			*NAED*			*Ex-use*	*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*			
Number of women-years	1194	1143	211	1354	13027	2811	16217	14972	46	33782
Self-reported depression	12	9	3	12	70	11	81	61	0	166
IR (95% CI)*	100.5 (52.1-175.0)	78.7 (36.1-148.9)	142.4 (29.5-410.5)	88.6 (45.9-154.3)	53.7 (41.9-67.8)	39.1 (19.6-69.9)	49.9 (39.7-62.0)	40.7 (31.2-52.3)	0.0 (0.0-774.7)	49.1 (42.0-57.2)
Thereof										
Confirmed	1	0	0	0	10	1	11	9	0	21
	8.4 (0.21-46.6)	0.0 (0.0-32.2)	0.0 (0.0-173.6)	0.0 (0.0-27.2)	7.7 (3.7-14.1)	3.6 (0.09-19.8)	6.8 (3.4-12.1)	6.0 (2.7-11.4)	0.0 (0.0-774.7)	6.2 (3.8-9.5)
Not confirmed	11	9	3	12	60	10	70	52	0	145
	92.2 (46.1-164.3)	78.7 (36.1-148.9)	142.4 (29.5-410.5)	88.6 (45.9-154.3)	46.1 (35.2-59.2)	35.6 (17.1-65.3)	43.2 (33.7-54.5)	34.7 (25.9-45.5)	0.0 (0.0-774.7)	42.9 (36.2-50.5)
Thereof										
Recurrent depression	0	0	1	1	5	2	7	4	0	12
	0.0 (0.0-30.9)	0.0 (0.0-32.2)	47.5 (1.2-261.6)	7.4 (0.19-41.1)	3.8 (1.2-9.0)	7.1 (0.86-25.7)	4.3 (1.7-8.9)	2.7 (0.73-6.8)	0.0 (0.0-774.7)	3.6 (1.8-6.2)
Potential depression, no further clarification possible	0	1	0	1	7	1	8	6	0	15
	0.0 (0.0-30.9)	8.7 (0.22-48.6)	0.0 (0.0-173.6)	7.4 (0.19-41.1)	5.4 (2.2-11.1)	3.6 (0.09-19.8)	4.9 (2.1-9.7)	4.0 (1.5-8.7)	0.0 (0.0-774.7)	4.4 (2.5-7.3)
Depression treated by GP	3	1	1	2	15	0	15	5	0	25
	25.1 (5.2-73.3)	8.7 (0.22-48.6)	47.5 (1.2-261.6)	14.8 (1.8-53.3)	11.5 (6.4-19.0)	0.0 (0.0-13.1)	9.2 (5.2-15.3)	3.3 (1.1-7.8)	0.0 (0.0-774.7)	7.4 (4.8-10.9)
Depressive disorders treated by psychologist	0	0	0	0	4	1	5	4	0	9
	0.0 (0.0-30.9)	0.0 (0.0-32.2)	0.0 (0.0-173.6)	0.0 (0.0-27.2)	3.1 (0.84-7.9)	3.6 (0.09-19.8)	3.1 (1.0-7.2)	2.7 (0.73-6.8)	0.0 (0.0-774.7)	2.7 (1.2-5.1)
Other psychiatric disorders**	0	1	0	1	3	0	3	2	0	6
	0.0 (0.0-30.9)	8.7 (0.22-48.6)	0.0 (0.0-173.6)	7.4 (0.19-41.1)	2.3 (0.47-6.7)	0.0 (0.0-13.1)	1.8 (0.38-5.4)	1.3 (0.16-4.8)	0.0 (0.0-774.7)	1.8 (0.65-3.9)
Other psychic problems***	8	6	1	7	25	6	31	28	0	74
	67.0 (29.0-131.6)	52.5 (19.3-113.9)	47.5 (1.2-261.6)	51.7 (20.8-106.3)	19.2 (12.4-28.3)	21.3 (7.8-46.4)	19.1 (13.0-27.1)	18.7 (12.4-27.0)	0.0 (0.0-774.7)	21.9 (17.2-27.5)
'No event'-before study, repetition	0	0	0	0	1	0	1	3	0	4
	0.0 (0.0-30.9)	0.0 (0.0-32.2)	0.0 (0.0-173.6)	0.0 (0.0-27.2)	0.77 (0.02-4.3)	0.0 (0.0-13.1)	0.62 (0.02-3.4)	2.0 (0.41-5.9)	0.0 (0.0-774.7)	1.2 (0.32-3.0)

Note: *Incidence rate is shown per 10^4 women-years.

Note: **Includes e.g. schizophrenia, bipolar, anxiety, eating disorders.

Note: ***Includes e.g. mood changes, psychosomatic disorders, no HCP visited.

Table 73: Incidence rate of self-reported depression, AT population, Ukraine

	DNG	*OAED*			*NAED*			*Ex-use*	*Allocation unknown*	*Total*
		GnRH-a	*Danazol*	*All OAED*	*CHC*	*Other progestins*	*All NAED*			
Number of women-years	417	200	502	702	1314	1380	2741	4439	66	8365
Self-reported depression	9	2	9	11	15	18	34	40		94
IR (95% CI)*	215.8 (99.2-405.7)	100.0 (12.1-356.4)	179.3 (82.3-337.6)	156.7 (78.5-278.6)	114.1 (64.0-187.6)	130.4 (77.5-205.3)	124.0 (86.0-172.9)	90.1 (64.4-122.5)	0 0.0 (0.0-547.6)	112.4 (90.9-137.3)
Thereof										
Confirmed	0 0.0 (0.0-88.1)	0 0.0 (0.0-182.7)	1 19.9 (0.50-110.5)	1 14.2 (0.36-79.1)	1 7.6 (0.19-42.3)	0 0.0 (0.0-26.7)	1 3.6 (0.09-20.3)	0 0.0 (0.0-8.3)	0 0.0 (0.0-547.6)	2 2.4 (0.29-8.6)
Not confirmed	9 215.8 (99.2-405.7)	2 100.0 (12.1-356.4)	8 159.4 (69.0-311.6)	10 142.4 (68.5-260.4)	14 106.5 (58.4-178.1)	18 130.4 (77.5-205.3)	33 120.4 (83.0-168.7)	40 90.1 (64.4-122.5)	0 0.0 (0.0-547.6)	92 110.0 (88.7-134.7)
Thereof										
Recurrent depression	0 0.0 (0.0-88.1)	0 0.0 (0.0-182.7)	0 0.0 (0.0-73.2)	0 0.0 (0.0-52.4)	1 7.6 (0.19-42.3)	3 21.7 (4.5-63.4)	4 14.6 (4.0-37.3)	3 6.8 (1.4-19.7)	0 0.0 (0.0-547.6)	7 8.4 (3.4-17.2)
Potential depression, no further clarification possible	2 48.0 (5.8-172.2)	0 0.0 (0.0-182.7)	2 39.8 (4.8-143.2)	2 28.5 (3.5-102.5)	0 0.0 (0.0-28.0)	2 14.5 (1.8-52.2)	2 7.3 (0.88-26.3)	5 11.3 (3.7-26.3)	0 0.0 (0.0-547.6)	11 13.1 (6.6-23.5)
Depression treated by GP	3 71.9 (14.9-208.8)	0 0.0 (0.0-182.7)	2 39.8 (4.8-143.2)	2 28.5 (3.5-102.5)	3 22.8 (4.7-66.6)	0 0.0 (0.0-26.7)	3 10.9 (2.3-32.0)	8 18.0 (7.8-35.5)	0 0.0 (0.0-547.6)	16 19.1 (10.9-31.0)
Depressive disorders treated by psychologist	0 0.0 (0.0-88.1)	0 0.0 (0.0-182.7)	0 0.0 (0.0-73.2)	0 0.0 (0.0-52.4)	0 0.0 (0.0-28.0)	1 7.2 (0.18-40.3)	1 3.6 (0.09-20.3)	1 2.3 (0.06-12.5)	0 0.0 (0.0-547.6)	2 2.4 (0.29-8.6)
Other psychiatric disorders**	0 0.0 (0.0-88.1)	0 0.0 (0.0-182.7)	0 0.0 (0.0-73.2)	0 0.0 (0.0-52.4)	0 0.0 (0.0-28.0)	1 7.2 (0.18-40.3)	1 3.6 (0.09-20.3)	3 6.8 (1.4-19.7)	0 0.0 (0.0-547.6)	4 4.8 (1.3-12.2)
Other psychic problems***	4 95.9 (26.2-243.8)	2 100.0 (12.1-356.4)	4 79.7 (21.8-202.8)	6 85.5 (31.4-185.1)	8 60.9 (26.3-119.6)	9 65.2 (29.9-123.4)	18 65.7 (39.0-103.6)	19 42.8 (25.8-66.8)	0 0.0 (0.0-547.6)	47 56.2 (41.3-74.6)
'No event'-before study, repetition	0 0.0 (0.0-88.1)	0 0.0 (0.0-182.7)	0 0.0 (0.0-73.2)	0 0.0 (0.0-52.4)	2 15.2 (1.8-54.9)	2 14.5 (1.8-52.2)	4 14.6 (4.0-37.3)	1 2.3 (0.06-12.5)	0 0.0 (0.0-547.6)	5 6.0 (1.9-13.9)

Note: *Incidence rate is shown per 10^4 women-years.

Note: **Includes e.g. schizophrenia, bipolar, anxiety, eating disorders.

Note: ***Includes e.g. mood changes, psychosomatic disorders, no HCP visited.

Annex 2.1-2.3 Description of anemia, depression and VTE cases under exposure
Not included into the public version