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Risk of depression and anemia in users of hormonal endometriosis treatments: Results from the VIPOS study

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ABSTRACT

Objective: Dienogest (DNG) 2 mg (Visanne) was launched for endometriosis treatment in Europe in 2010. The Visanne Post-approval Observational Study (VIPOS) was designed to assess the safety of DNG 2 mg/day compared to other hormonal endometriosis treatments, focusing especially on clinically relevant depression and anemia.

Study design: Large, prospective, non-interventional, active surveillance study in six European countries. Participants were recruited via gynecologists or specialized centers routinely prescribing endometriosis medication. Self-administered questionnaires during study entry and follow-up collected information on baseline characteristics, health status and endometriosis treatment. Patient-reported anemia and depression cases were validated by health care professionals. Inferential statistics were based on Cox proportional hazards models and crude and adjusted hazard ratios (HR) between cohorts were calculated (including 95% confidence intervals [CI]). Adjustment for potential confounding was performed by including predefined prognostic factors as covariates in the Cox models.

Results: Out of 26,430 participants, 11.4% used DNG, 12.8% used other approved endometriosis medications (OAED) and 75.7% used hormonal treatments not approved but frequently used for endometriosis treatment (NAED). At baseline, DNG users more frequently reported a surgically confirmed endometriosis diagnosis, severe endometriosis-associated pain and a history of depression, compared to the other cohorts. Baseline characteristics showed large inter-country variability.

Overall, the number of confirmed anemia and depression events were substantially lower than expected. The adjusted HRs for anemia 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. The adjusted HRs for new or worsening depression 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.

Conclusion: The main limitations encountered (low number of confirmed events and considerable inter-country variability) made a robust statistical analysis and a solid interpretation of the results challenging. However, no safety signal regarding anemia for DNG users could be detected, whereas a slight increase in depression risk cannot be excluded but might be explained by baseline severity of endometriosis or unknown country-specific confounding variables. VIPOS reflected routine use of hormonal endometriosis medications and provided real-world insights into endometriosis management in Europe.

Introduction

Endometriosis, one of the most common gynecologic disorders, is characterized by the ectopic growth of endometrial tissue outside the uterine cavity. It affects around 10% of women of reproductive age and clinical signs typically involve a combination of chronic pelvic pain, menstrual irregularities, dysmenorrhea, dyspareunia and infertility [1]. There appears to be a negative feedback cycle associated with endometriosis and mental well-being, as the symptoms of endometriosis often affect psychological and social functioning. *Vice versa*, psychological factors play an important role in determining the severity of symptoms and the

Abbreviations: CHC, combined hormonal contraceptives; CI, confidence interval; DNG, dienogest; GnRH-a, gonadotropin-releasing hormone agonists; HR, hazard ratio; IR, incidence rate; NAED, medications not approved but frequently prescribed for endometriosis treatment; OAED, other medications approved for the treatment of endometriosis; VIPOS, Visanne post-approval observational study; WY, women-years.

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effectiveness of treatments [2]. Given this, it is not surprising that endometriosis is associated with an elevated likelihood of developing depression and anxiety disorders [3–6]. The literature suggests that around 20% of women with endometriosis suffer from depression [5,7,].

Psychiatric comorbidities associated with endometriosis are highly correlated with the experience of pelvic pain, rather than of endometriosis itself. Moreover, pain perception can be independent of the severity of endometriosis [9–11]. This suggests that psychological factors may be involved, which influence pain experience in women with endometriosis and it has been demonstrated that high levels of anxiety and depression can amplify pain severity [12,13]. Thus, a vicious cycle might be initiated, where endometriosis-related pain causes anxiety and depression, which in turn amplifies pain perception and causes even more psychological distress, leading to a severe reduction of women's quality of life and a potential decrease of treatment success [7,14].

Heavy menstrual bleeding (menorrhagia) is another common symptom associated with endometriosis and in rare cases, even chronic hemorrhagic ascites can appear [15]. These bleeding disorders can potentially contribute to clinically relevant anemia. Based on the literature, the prevalence of anemia in premenopausal European women is approximately 10–15%.

Several treatment options for endometriosis do exist, including analgesic or hormonal therapies, and surgery [1,16]. While several endometriosis medications are effective in decreasing pelvic pain, many are associated with suboptimal safety and tolerability, limiting their duration of use. On the other hand, several progestins that provide long-term efficacy can have side effects such as weight gain or androgenic effects [17]. Dienogest (DNG) is a 19-nortestosterone derivative progestin that is highly selective for progesterone receptors and is known for having strong endometrial effects. Visanne (DNG 2 mg) leads to a reduction of endometriosis-associated pain and was launched in 2010 for endometriosis treatment in Europe. Benefits offered by DNG 2 mg include potent progestogenic effects causing endometrial lesion reduction, while suppressing estrogen levels only moderately [17–19].

An ongoing concern associated with progestogens has been their potential role in influencing mood disturbances and depression and contrasting results regarding this issue have been published [20,21].

Changes in bleeding pattern are another well-recognized side effect of many progestins [17,22]. In particular, a 52-week open-label study in Japan reported inter-menstrual spotting or bleeding as a side-effect of DNG 2 mg in 72% of women [23].

Given the complexities of the potential interaction between progestogens, endometriosis, depression and anemia, a study assessing the risk of anemia and depression in women receiving medical treatment for endometriosis was needed. The Visanne Post-approval Observational Study (VIPOS) was designed to assess the safety of DNG 2 mg in comparison to other hormonal endometriosis treatments in a real-world setting, with a special focus on clinically relevant depression and anemia.

Methods

Study design, setting and cohorts

VIPOS was a prospective, observational, long-term cohort study in six European countries (Germany, Switzerland, Russia, Poland, Ukraine, and Hungary) conducted between 2010 and 2018. Three main cohorts were followed: (1) users of Visanne (DNG), (2) users of other medications approved for the treatment of endometriosis (OAED), such as Gonadotropin-releasing hormone agonists (GnRH-a) and danazol, and (3) users of hormonal medications not approved but frequently prescribed for endometriosis treatment (NAED), mainly combined hormonal contraceptives (CHC) and other progestins. All cohorts consisted of women starting a new hormonal endometriosis treatment. The study did not interfere with the usual prescribing behavior of gynecologists and specialized endometriosis centers or with the individual needs of the participants, thus no medical inclusion or exclusion criteria were applied. However, women not willing to participate in a long-term follow-up or those with language barriers were not eligible for inclusion. All study participants completed a baseline questionnaire and were then actively contacted after 6, and then every 12 months. Total follow-up time was up to 84 months, depending on the time of recruitment. Due to the low number of women enrolled in Switzerland, data from these women are part of the overall data only. A small group of study participants used more than one hormonal endometriosis medication concomitantly; these were classified as "allocation unknown".

Variables and validation process

VIPOS was designed to evaluate the safety of DNG 2 mg/day compared with other hormonal treatments with respect to the occurrence of anemia induced by cyclical bleeding disturbances and newly diagnosed or worsening depression. All self-reported anemia and depression cases were validated based on pre-defined criteria and verified by blinded independent adjudication. A depression event was only confirmed if it was judged as such by a physician specialized in psychiatry or if a suicide (attempt) occurred. An anemia event was only confirmed if it was verified by a physician, reliable laboratory tests or a pertinent therapy and no explanation other than endometriosis was identified.

Statistical methods

Based on a 10–15% background prevalence of anemia in premenopausal European women [24], the sample size calculation was based on an incidence of 0.01 (100 events/10,000 women-years [WY]). The expected incidence rate (IR) for newly diagnosed or worsening depression was at least 0.01 (100 events/10,000 WY) based on an estimated prevalence rate of 20% for depression in women with endometriosis [5,7,]. Power calculations showed that approximately 84,000 WY were sufficient to demonstrate non-inferiority of DNG vs OAED for anemia and depression. Accordingly, the study was powered to exclude a two-fold risk of anemia and 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.

Statistical analyses were conducted based on the prescribed medication for the description of baseline characteristics and data on outcomes during follow-up were assigned to the medication used at the time of the event.

Baseline population characteristics were described by absolute and relative numbers per (sub-) cohort and basic summary statistics were applied. Primary outcome data was expressed as IR. Exact 95% confidence intervals (CI) were calculated. Inferential statistics for anemia and depression were based on Cox proportional hazards models and crude and adjusted hazard ratios (HR) between cohorts were calculated. Adjustment for potential confounding was performed by including predefined prognostic factors as covariates in the Cox models (for depression: age, personal/family history of depression and previous use of antidepressants; for anemia: age, history of bleeding disorders and history of treated anemia). Country was considered a random

Table 1
Selected baseline characteristics per (sub-) cohort.

	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%)	16,638 (100%)	3246 (100%)	20,016 (100%)	20 (100%)	26,430 (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
Diagnosis classification									
Diagnosis based on clinical symptoms	1608 (53.2%)	1747 (68.7%)	797 (96.1%)	2544 (75.5%)	15,974 (96.0%)	2967 (91.4%)	19,057 (95.2%)	18 (90.0%)	23,227 (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%)
Pain severity score									
Mild (0–3)	849 (28.1%)	660 (26.0%)	88 (10.6%)	748 (22.2%)	7605 (45.7%)	1057 (32.6%)	8722 (43.6%)	3 (15.0%)	10,322 (39.1%)
Moderate (4–7)	1462 (48.4%)	1450 (57.0%)	638 (77.0%)	2088 (61.9%)	7389 (44.4%)	1857 (57.2%)	9296 (46.4%)	16 (80.0%)	12,862 (48.7%)
Severe (8–10)	575 (19.0%)	350 (13.8%)	97 (11.7%)	447 (13.3%)	1315 (7.9%)	239 (7.4%)	1563 (7.8%)	1 (5.0%)	2586 (9.8%)
Missing	137 (4.5%)	82 (3.2%)	6 (0.7%)	88 (2.6%)	329 (2.0%)	93 (2.9%)	435 (2.2%)	0 (0.00%)	660 (2.5%)
Endometriosis associated symptoms									
Pelvic pain	1558 (51.5%)	1329 (52.3%)	594 (71.7%)	1923 (57.0%)	4872 (29.3%)	1443 (44.5%)	6360 (31.8%)	12 (60.0%)	9853 (37.3%)
Pain during or after sexual intercourse	1164 (38.5%)	950 (37.4%)	434 (52.4%)	1384 (41.1%)	3207 (19.3%)	1153 (35.5%)	4382 (21.9%)	3 (15.0%)	6933 (26.2%)
Painful periods	2034 (67.3%)	1598 (62.9%)	671 (80.9%)	2269 (67.3%)	10,280 (61.8%)	1758 (54.2%)	12,089 (60.4%)	12 (60.0%)	16,404 (62.1%)
Difficulty conceiving / infertility	686 (22.7%)	673 (26.5%)	186 (22.4%)	859 (25.5%)	1653 (9.9%)	827 (25.5%)	2489 (12.4%)	5 (25.0%)	4039 (15.3%)
Heavy or irregular bleeding	1430 (47.3%)	1120 (44.1%)	583 (70.3%)	1703 (50.5%)	8522 (51.2%)	1660 (51.1%)	10,263 (51.3%)	19 (95.0%)	13,415 (50.8%)
Tiredness / weakness	1329 (44.0%)	821 (32.3%)	178 (21.5%)	999 (29.6%)	3850 (23.1%)	971 (29.9%)	4877 (24.4%)	5 (25.0%)	7210 (27.3%)
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	37 (1.2%)	13 (0.5%)	1 (0.1%)	14 (0.4%)	55 (0.3%)	17 (0.5%)	72 (0.4%)	0 (0.00%)	123 (0.5%)
Family history of endometriosis*	397 (13.1%)	285 (11.2%)	36 (4.3%)	321 (9.5%)	3132 (18.8%)	657 (20.2%)	3807 (19.0%)	1 (5.0%)	4526 (17.1%)
Family history of depression*	285 (9.4%)	154 (6.1%)	13 (1.6%)	167 (5.0%)	1382 (8.3%)	466 (14.4%)	1854 (9.3%)	1 (5.0%)	2307 (8.7%)

Note: *First-degree relatives only.

source of variance and was included as a stratum into the Cox model.

Results

Participants

A total of 27,840 women were enrolled in the study. Thereof, 1410 did not start with their baseline medication and were thus excluded from the here reported analysis of primary outcomes. Overall, 63% were treated with combined hormonal contraceptives, 11.4% with DNG 2 mg, 12.3% with other progestins, 9.6% with GnRH-a and 3.1% with danazol.

Descriptive data

The number of study participants and descriptive statistics of patient characteristics, personal and family medical history, and endometriosis-related symptoms are displayed in Table 1 (by [sub-]cohort) and Table 2 (by country).

Overall, baseline characteristics were similar between the DNG and the OAED cohorts, whereas the NAED cohort in comparison showed a lower mean age, less frequent severe endometriosis-related symptoms and a mostly symptom-based (not surgically confirmed) diagnosis (Table 1). The overall mean age of study participants was 32.9 ± 8.96 years (DNG: 35.1 ± 7.70; OAED: 37.0 ± 8.19; NAED: 31.9 ± 9.01). When sub-classified by country, the youngest participants came from Hungary with a mean age of 27.5 ± 7.55 years and the oldest from Ukraine with a mean age of 36.9 ± 7.91 years. The most evident differences between the DNG cohort and the other cohorts were a more frequent surgically confirmed endometriosis diagnosis (46.8%), a more severe endometriosis-associated pain (19.0% pain score 8–10[1]) and a more frequent history of depression (5.3%) and anti-depressant use (1.2%).

Notably, baseline characteristics showed a large inter-country variability (Table 2). Differences between countries were found in the reporting of severe endometriosis-related pain and personal/family history of depression, which were both most frequently described by women from Poland and Germany and least frequently by women from Russia and Ukraine. Furthermore, prescription patterns of endometriosis medications varied considerably between countries (Suppl. Table 1).

Main results

IRs of self-reported and confirmed cases of anemia (Fig. 1) and depression (Fig. 2) varied widely across countries. The highest IR for confirmed anemia was observed in Poland (43.5/10,000 WY)

[1] Women could report their pain on a scale from 0 (no pain) to 10 (unbearable). Pain severity was subsequently categorized into mild (score 0–3), moderate (score 4–7) or severe (score 8–10)

Table 2
Selected baseline characteristics per country.

	Germany	Poland	Hungary	Switzerland	Russia	Ukraine	Total
Number (%) of women	1717 (100%)	954 (100%)	8287 (100%)	74 (100%)	13,008 (100%)	2390 (100%)	26,430 (100%)
Age (years)							
Mean	31.1	31.6	27.5	30.1	36.0	36.9	32.9
SD	9.79	8.03	7.55	6.99	8.12	7.91	8.96
Diagnosis classification							
Diagnosis based on clinical symptoms	1066 (62.1%)	611 (64.0%)	7251 (87.5%)	25 (33.8%)	12,242 (94.1%)	2032 (85.0%)	23,227 (87.9%)
Diagnosis confirmed by surgery	651 (37.9%)	343 (36.0%)	1036 (12.5%)	49 (66.2%)	766 (5.9%)	358 (15.0%)	3203 (12.1%)
Pain severity score							
Mild (0–3)	424 (24.7%)	204 (21.4%)	5053 (61.0%)	8 (10.8%)	3888 (29.9%)	745 (31.2%)	10,322 (39.1%)
Moderate (4–7)	862 (50.2%)	436 (45.7%)	2532 (30.6%)	33 (44.6%)	7613 (58.5%)	1386 (58.0%)	12,862 (48.7%)
Severe (8–10)	367 (21.4%)	276 (28.9%)	603 (7.3%)	30 (40.5%)	1081 (8.3%)	229 (9.6%)	2586 (9.8%)
Missing	64 (3.7%)	38 (4.0%)	99 (1.2%)	3 (4.1%)	426 (3.3%)	30 (1.3%)	660 (2.5%)
Endometriosis associated symptoms							
Pelvic pain	769 (44.8%)	520 (54.5%)	1741 (21.0%)	40 (54.1%)	5330 (41.0%)	1453 (60.8%)	9853 (37.3%)
Pain during or after sexual intercourse	479 (27.9%)	335 (35.1%)	1212 (14.6%)	44 (59.5%)	3883 (29.9%)	980 (41.0%)	6933 (26.2%)
Painful periods	1271 (74.0%)	671 (70.3%)	4353 (52.5%)	59 (79.7%)	8321 (64.0%)	1729 (72.3%)	16,404 (62.1%)
Difficulty conceiving / infertility	214 (12.5%)	142 (14.9%)	366 (4.4%)	18 (24.3%)	2844 (21.9%)	455 (19.0%)	4039 (15.3%)
Heavy or irregular bleeding	742 (43.2%)	528 (55.3%)	4230 (51.0%)	34 (45.9%)	6385 (49.1%)	1496 (62.6%)	13,415 (50.8%)
Tiredness / weakness	515 (30.0%)	396 (41.5%)	2056 (24.8%)	43 (58.1%)	3253 (25.0%)	947 (39.6%)	7210 (27.3%)
Personal history of depression	176 (10.3%)	41 (4.3%)	221 (2.7%)	13 (17.6%)	123 (0.9%)	50 (2.1%)	624 (2.4%)
Personal history of anemia	95 (5.5%)	44 (4.6%)	415 (5.0%)	9 (12.2%)	773 (5.9%)	151 (6.3%)	1487 (5.6%)
Use of Antidepressants/SSRI	46 (2.7%)	11 (1.2%)	55 (0.7%)	6 (8.1%)	4 (0.03%)	1 (0.04%)	123 (0.5%)
Endometriosis of relatives*	194 (11.3%)	90 (9.4%)	2107 (25.4%)	6 (8.1%)	1914 (14.7%)	215 (9.0%)	4526 (17.1%)
Depression of relatives*	261 (15.2%)	74 (7.8%)	808 (9.8%)	30 (40.5%)	1068 (8.2%)	66 (2.8%)	2307 (8.7%)

Note: *First-degree relatives only.

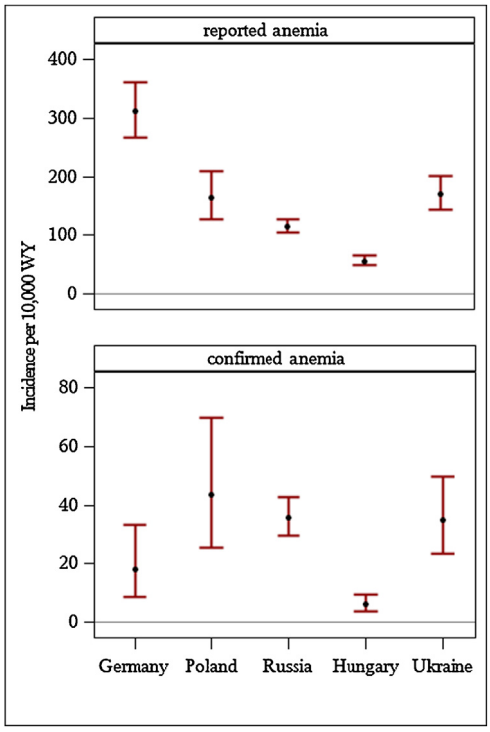

Fig. 1. Incidence rates of self-reported and confirmed anemia by country.

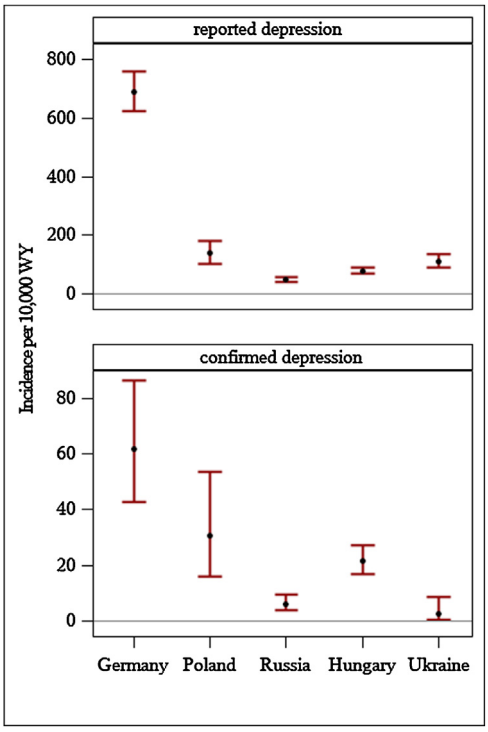

Fig. 2. Incidence rates of self-reported and confirmed depression by country.

and the lowest in Hungary (6.1/10,000 WY), whereas the highest IR for confirmed depression was reported in Germany (61.8/10,000 WY) and the lowest in Ukraine (2.4/10,000 WY). Overall, IRs of confirmed events, obtained upon application of the pre-defined validation criteria, were substantially lower than expected based on the literature. Table 3 displays the number of events, IRs and (crude/adjusted) HRs of confirmed anemia cases by cohort and Table 4 the respective data for depression. The overall IR of anemia was 23.4 per 10,000 WY (197 confirmed cases). The IRs per user cohort were as follows: DNG (33.5/10,000 WY; 15 cases); OAED (49.1/10,000 WY; 12 cases); NAED (22.9/10,000 WY; 92 cases). The adjusted HRs were close to unity (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). However, due to the low number of events, a two-fold risk of anemia in DNG users vs OAED and NAED could not be excluded. Instead, a threefold risk for these comparisons could be excluded.

Overall, 139 (new or worsening) depression cases were confirmed. The IR in DNG users was higher (35.7/10,000 WY; 16 cases) compared to OAED (8.2/10,000 WY; 2 cases) and NAED users (17.0/10,000 WY; 68 cases). The adjusted HRs were 1.8 (95% CI, 0.3–9.4) for

Table 3
Number of events, incidence rates and hazard ratios of confirmed anemia cases by cohort.

Cohorts	No. of events	WY	Incidence per 10^4 WY	Crude hazard ratio (95% CI)	Adjusted hazard ratio* (95% CI)
DNG	15	4482	33.47	0.99	1.06
OAED	12	2444	49.10	(0.40–2.47)	(0.42–2.64)
DNG	15	4482	33.47	1.35	1.34
NAED	92	40,090	22.95	(0.75–2.44)	(0.74–2.44)

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

Table 4
Number of events, incidence rates and hazard ratios of confirmed depression cases by cohort.

Cohorts	No. of events	WY	Incidence per 10^4 WY	Crude hazard ratio (95% CI)	Adjusted hazard ratio* (95% CI)
DNG	16	4482	35.70	1.89	1.80
OAED	2	2444	8.18	(0.37–9.70)	(0.34–9.38)
DNG	16	4482	35.70	1.57	1.51
NAED	68	40,090	16.96	(0.88–2.80)	(0.81–2.80)

Note: *Adjusted for age, family and personal history of depression and use of antidepressants.

DNG vs OAED and 1.5 (95% CI, 0.8–2.8) for DNG vs NAED. Although the results did not allow for a two-fold risk for depression to be excluded, the adjusted HR 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 3.

Comment

The VIPOS study was designed to assess the safety of Visanne (DNG 2 mg), OAED and NAED. At baseline, the NAED cohort differed from the other cohorts by a lower mean age, less severe endometriosis symptoms and a mostly symptom-based diagnosis. This difference could be expected, as patients prescribed with a non-approved medication, such as a CHC, and diagnosed solely based on symptoms, tend to have a less severe phenotype. In contrast, women with a surgical diagnosis are usually older and have a more severe form of the disease, since they have often experienced a long delay between onset of symptoms and final diagnosis [25]. The overall low rate of surgical confirmation in all cohorts might represent the recently observed trend of limiting surgical procedures in favor of medical therapy prior to or in the absence of a laparoscopic confirmation [25]. Furthermore, ongoing efforts are directed towards the development and validation of non-invasive diagnostic procedures [32].

Notably, among all cohorts, endometriosis diagnosis of DNG users was most often surgically confirmed, hinting at the possibility that these women had a more severe form of the disease at baseline. In line with this, women taking DNG reported the highest pain intensity. DNG users also more frequently reported a personal history of depression and a slightly higher use of anti-depressants.

In addition to these differences in disease severity and medical history between cohorts, there was considerable inter-country variance in several baseline parameters, such as pain severity. This might reflect a potential impact of country-specific socio-cultural and economic factors on women's subjective reporting of pain-related symptoms. A literature overview [26] addressing the influence of socio-cultural contexts on the experience of pain reported a clear correlation between pain perception and ethnic/social background [27–30].

Overall, the number and IRs of self-reported depression and anemia events were close to those estimated based on the literature [5,7,24]. However, upon applying the pre-determined validation criteria, the number and IRs of confirmed events in all user cohorts were substantially lower than expected, making a solid interpretation of the results difficult. Despite this, the adjusted HRs for anemia of DNG vs OAED and DNG vs NAED did not reveal any increased risk for DNG users. With regards to depression, adjusted HRs were slightly increased for DNG when compared to OAED and NAED. Although a real increased risk for DNG cannot be excluded, an explanation for this result might be the potentially more severe form of endometriosis in DNG users at baseline.

IRs of reported and confirmed anemia and depression events varied widely across countries. This can potentially be explained by the presence of country-specific additional confounding variables, such as the women's socio-cultural background. In Germany, where a high baseline pain severity was reported, the highest number of depression events were reported during follow-up, whereas Russia and Ukraine reported only mild pain at baseline and the lowest number of depression events during follow-up. Thus, inter-country variance in pain perception and coping might have been influencing the primary outcome. Furthermore, differences in prescription patterns between countries were observed and hint at varying diagnostic and treatment schemes among countries. In accordance with the real-world non-interventional study design, the prescription choice was not influenced and reflects routine clinical practice in the respective countries.

In order to account for the inter-country variability, a stratification by country was built into the Cox model. However, due to the low incidence of confirmed events, the power of the study was insufficient to exclude a two-fold risk of newly diagnosed or deteriorating depression for DNG vs OAED or NAED. Regarding anemia, a threefold risk in DNG users vs OAED or NAED could be excluded, implying no safety signal with respect to bleeding disorders.

The VIPOS study benefited from several strengths which minimized the effects of bias and confounding. Among these were: a prospective, comparative cohort design; the availability of important confounder information; the validation of outcomes of interest; an independent, blinded adjudication; and relevant statistical analyses.

However, the possibility of residual confounding can never be completely eliminated in observational studies [31]. A potential limiting factor of VIPOS was the unequal geographic distribution of study participants, with the majority of women coming from Eastern Europe, where guidelines and clinical practice might differ from the rest of Europe. VIPOS was designed as an "all-comer" study, i.e. study participants were eligible if prescribed a new hormonal endometriosis medication irrespective of the type of medication, type of diagnosis or other criteria, in order to describe real-world user populations of the respective medications. In

addition, enrolment of participants via the different study sites was competitive (no limit was imposed upon the single study sites) and patients were consecutively recruited until the necessary sample size was reached. This and the dependence of the study start on the time-delayed Visanne launches in the individual countries, contributed to an unequal distribution of women among the participating countries.

A further limiting factor was the lack of information on socio-cultural factors which could have influenced the occurrence of depression.

Conclusions

Overall, the main limitations encountered (low number of confirmed events and considerable inter-country variability) made a robust statistical analysis and thus a solid interpretation of the results challenging. However, we can conclude no safety signal regarding anemia for DNG users, whereas a slight increase in depression risk cannot be excluded but might be explained by baseline severity of endometriosis or unknown confounding variables. The VIPOS study reflected routine use of hormonal endometriosis medications and provided new real-world insights into endometriosis management in Europe.

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Declaration of Competing Interest

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