27 October 2022
EMA/PRAC/897622/2022
Pharmacovigilance Risk Assessment Committee (PRAC)

Signal assessment report on heavy menstrual bleeding with tozinameran / Comirnaty (COVID-19 mRNA vaccine)

EPITT no: 19783

Procedure no: SDA 053.1

Confirmation assessment report	04 February 2022
Adoption of first PRAC recommendation	10 February 2022
Preliminary assessment report on additional data	16 May 2022
Deadline for comments	30 May 2022
Updated rapporteur assessment report	03 June 2022
Adoption of second PRAC recommendation	10 June 2022
Preliminary assessment report on additional data	03 Oct 2022
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Updated rapporteur assessment report	20 Oct 2022
Adoption of third PRAC recommendation	27 Oct 2022

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Active substance(s) (invented name)	Tozinameran / Comirnaty (COVID-19 mRNA vaccine)
Marketing authorisation holder(s)	BioNTech Manufacturing GmbH
Authorisation procedure	
☒	Centralised
☐	Mutual recognition or decentralised
☐	National

Adverse event/reaction:	Heavy menstrual bleeding

Signal validated by:	NO
Date of circulation of signal validation report:	
Signal confirmed by:	NL
Date of confirmation:	04-02-2022
PRAC Rapporteur appointed for the assessment of the signal:	David Benee Olsen (NO)

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1. Background

The broad clinical issue of "menstrual disorders" was reviewed in the 9th MSSR for Comirnaty. The conclusion by the PRAC Rapporteur in the 9th Monthly Summary Safety report with a DLP of 31 August 2021 was the following: "It is therefore agreed with the MAH that currently the data do not support a safety issue. Closure of this safety signal is accepted."

However, the issue of menstrual disturbances is somewhat difficult to analyse, due to the range of clinical entities included, the difficulty in estimating their background incidences in relevant populations and the fact that reports are mainly from patients and lacking thorough clinical evaluation. Given the many different symptoms and reactions included in the topic "Menstrual disorders", the signalling MS NO finds it necessary to extract those reactions/patterns that we consider the most severe and evaluate these in separate signal procedures. This would make the assessment more tailored to the reactions in question.

The signalling MS NO believes that a new evaluation beyond routine pharmacovigilance is currently warranted, mainly for the following reasons:

1. The data have changed. Since the time of the 9th MSSR uAR Norway has received an increased numbers of reports of heavy menstrual bleeding. Most women of reproductive age (18-54 years) in Norway were vaccinated from the beginning of summer 2021 and onwards. (Per 31.05.21 312 849 doses of Comirnaty had been given to women aged 18 – 54. Per 15.11.21 the exposure was 1 612 192, *i.e.*, it had increased by a tenfold. The total population is 5.4 million. Because of the time that has passed since the 9th MSSR uAR more reports of heavy menstrual bleedings have been received.

2. The time that has elapsed since the DLP of the 9th MSSR (31 Aug 2021) and the volume of reports. The number of post- marketing reports included in the review were 16 263. A more recent search in Vigibase per 14.01.22 yields a result of 81 602 reports globally within the HLGT 'Menstrual cycle and uterine bleeding', same search criteria as used by the MAH, *i.e.* the increase in number is substantial. We have gained more knowledge through an increased number of reports, which also means more qualitative information/details.

3. Based on our own ICSRs, we are under the impression that menstrual disorders are by far the most commonly reported ADRs from women. However, we do not have absolute numbers, due to a large volume of non-serious cases in backlog. Most of the reports of menstrual disorders are non-serious. In Norway, 4,2 million doses of Comirnaty and approximately 1 million doses of Spikevax has been given to women. NoMA has currently received approximately 50 000 ICSRs in total after vaccination with the COVID-19 vaccines, 81% from women. We estimate through manual sampling and screening of incoming reports since June when the signal/issue was first raised nationally, that approximately 30% of reports received by women could be related to the issue of menstrual disturbances. The large amount of these reports, relative to the total amount of reports, is a new aspect that warrants our attention.

Normally, a menstrual bleeding lasts around 2-7 days, and women lose about 3 to 5 tablespoons of blood in a period.

Some reports are categorised as serious due to the long duration or due to hospitalisation. The blood loss has in some cases led to syncope, treatment with iron and blood transfusion(s).

mRNA vaccines have been shown to be highly reactogenic and this could be a biologically plausible explanation through secondary stress on the hormonal system.

COVID-19 vaccination is a powerful immune stimulant. It is therefore plausible that the sensitive immune system of the endometrium is briefly modified by vaccination, thus potentially leading to menstrual disorders. However, no systematic investigations of the effect of COVID-19 vaccination on endometrial function have been carried out to date. A study designed specifically to investigate this relationship is currently ongoing at the Johns Hopkins Department of Gynecology and Obstetrics in the USA [1]

General comments PRAC Rapporteur:

Regarding (absolute) number of reports

It is acknowledged that the absolute number of spontaneously reported cases is high, but this not unexpected taking into account the huge background incidence of menstrual disorders irrespective of COVID-19 vaccination, and the pandemic context with an unprecedented high number of administered doses of vaccines, and the large (social) media attention on this topic.

Spontaneous reporting rates should be interpreted cautiously, as both underreporting and stimulated reporting [due to media attention] cannot be excluded.

The observed differences in reporting rates between different vaccines should be interpreted cautiously. Although in the analysis of the NL cases reporting menstrual disorders Lareb adjusted for age group, other characteristics may differ between vaccines due to prioritization per targeted populations/risk groups (*e.g.* health care workers, subjects with comorbidities, healthy young adults).

Confounding by (pre-)vaccination anxiety-/lockdown stress, undetected (corona)infections cannot be fully excluded at this moment.

Regarding the adverse event(s)

Menstrual disorders, *i.e.* changes in menstrual bleeding pattern are diverse and quite common among women, which hampers establishing a causal relation between the reported adverse event and vaccination. Symptoms are diverse (heavy menstrual bleeding [menorrhagia], amenorrhoea, oligomenorrhoea or irregular and intermenstrual blood loss) and, irrespective of vaccination, reported prevalence and incidence are varying per symptom from 6-90%. Consequently, it is challenging to assess whether the observed incidence of adverse events following vaccination would exceed the expected background incidence.

In addition abnormal uterine bleeding can have diverse underlying causes (*e.g.* Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia of the uterus, blood coagulopathies, Ovulatory dysfunction [polycystic ovarian syndrome, metabolic syndrome], Endometrial dysfunction, thyroid malfunction, pituitary tumor, Iatrogenic, and "Not otherwise classified" [medication, infections, stress]) which should be carefully evaluated and excluded when assessing a potential causal role of the vaccine. Examples of medication are hormonal contraception, aldosterone receptor-antagonists, chemotherapy, antipsychotics, antidepressants, antiepileptics, antiallergic drugs (centrally acting), life style drug (cocaine).

Further, stress, excessive exercise, and low body weight can interfere with the menstrual bleeding pattern.

Further, when hormonal contraception is used concomitantly, it's use will have replaced the natural menstrual bleeding pattern by a withdrawal bleeding. Further, the use of an iron IUD will also will have changed the normal menstruation pattern. Therefore, the background use of contraception needs to be

taken into account.

Clinical Study Data extracted from Comirnaty registration dossier

In the pivotal randomized clinical trial for Comirnaty the number of observed menstrual cycle abnormalities adverse events was balanced between placebo and active arms.

The clinical database for the pivotal efficacy study C4591001 was searched for all BNT162b2 adverse event reports with Preferred Terms classified within the High-Level Group Term (HLGT) of *Menstrual cycle and uterine bleeding disorders* (MedDRA version 24.0). The dataset used included data collected during the blinded follow-up period for all Phase 2/3 participants ≥16 years of age who received at least 1 dose of study intervention (Safety Population). Results reported include only data reported before the blind break for each participant. Therefore, because the exposure time (from Dose 1 to the end of blinded follow-up) varies by participant, the AE results are reported as incidence rate (IR) per 100 person-years (PY) of blinded follow-up. The overall dataset had a cutoff date of 13 March 2021.

During the placebo-controlled follow-up, adverse events coding to the HLGT Menstrual cycle and uterine bleeding disorders were reported for 12 participants in the BNT162b2 group and for 13 participants in the placebo group, corresponding to IRs of 0.14 per 100 PY and 0.16 per 100 PY, respectively (Table 1). These results show very low incidence and no imbalance in reporting incidence between the BNT162b2 and placebo groups.

Table 1. Incidence Rates of at Least 1 Menstrual Irregularity Adverse Event from Dose 1 to Unblinding Date, by Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

	Vaccine Group (as Administered)							
	BNT162b2 (30 µg) (N[a]=21926, TE[b]=83.4)			Placebo (N[a]=21921, TE[b]=82.2)			Difference	
Preferred Term	n[c]	IR (/100 PY)[d]	(95% CI[e])	n[c]	IR (/100 PY)[d]	(95% CI[e])	IRD (/100 PY)[f]	(95% CI[g])
Any event	12	0.14	(0.07, 0.25)	13	0.16	(0.08, 0.27)	-0.01	(-0.13, 0.10)
Amenorrhoea	2	0.02	(0.00, 0.09)	3	0.04	(0.01, 0.11)	-0.01	(-0.07, 0.04)
Dysfunctional uterine bleeding	1	0.01	(0.00, 0.07)	0	0.00	(0.00, 0.04)	0.01	(-0.01, 0.04)
Dysmenorrhoea	4	0.05	(0.01, 0.12)	3	0.04	(0.01, 0.11)	0.01	(-0.05, 0.07)
Menometrorrhagia	1	0.01	(0.00, 0.07)	0	0.00	(0.00, 0.04)	0.01	(-0.01, 0.04)
Menorrhagia	1	0.01	(0.00, 0.07)	2	0.02	(0.00, 0.09)	-0.01	(-0.05, 0.03)
Menstruation delayed	0	0.00	(0.00, 0.04)	2	0.02	(0.00, 0.09)	-0.02	(-0.06, 0.01)
Menstruation irregular	2	0.02	(0.00, 0.09)	0	0.00	(0.00, 0.04)	0.02	(-0.01, 0.06)
Metrorrhagia	2	0.02	(0.00, 0.09)	2	0.02	(0.00, 0.09)	-0.00	(-0.05, 0.05)
Premenstrual syndrome	0	0.00	(0.00, 0.04)	1	0.01	(0.00, 0.07)	-0.01	(-0.04, 0.01)

Note: MedDRA (v23.1) coding dictionary applied.
Note: The 95% confidence interval quantifies the precision of the incidence rate difference estimate. Confidence intervals are not adjusted for multiplicity. They should only be used to identify potentially important adverse events.
a. N = number of subjects in the specified group.
b. TE = total exposure time in 100 person-years across all subjects in the specified group. Exposure time for a subject is the time from Dose 1 to the end of blinded follow-up. This value is the denominator for the incidence rate calculation.
c. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
d. Incidence rate (IR) is calculated as number of subjects reporting the event/total exposure time in 100 person-years (PY) across all subjects in the specified group.
e. 2-sided CI based on Poisson distribution.
f. Difference in incidence rate (BNT162b2 [30 µg] - placebo).
g. 2-sided Wald CI for the incidence rate difference.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (20:15) Source Data: adae Table Generation: 14MAY2021 (06:36)
(Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: ./nda2_unblinded/C4591001_BLA_RR/adae_s131_aemi_p3_saf

2. Initial evidence

2.1. Signal validation

Highlights

- Seriousness: Some reports are categorised as serious due to the long duration or due to hospitalisation. The blood loss has in some cases led to syncope, treatment with iron and blood transfusion(s), which has also been reported in children.
- Evidence: A cohort study conducted by the Norwegian Institute of Public Health concludes that there is an increase in the incidence of menstrual changes among young women (aged 18 – 30) after vaccination against coronavirus, according to initial findings from population studies (N = 6000).
- Positive rechallenge cases.
- NoMA has fully processed 787 cases belonging to the PT 'heavy menstrual bleeding' as of 3 JAN 22. Globally there are 24, 832 ICSRs for PT 'heavy menstrual bleeding' per 14 JAN 22 in Vigibase.
- ROR: The IC025 for PT 'Heavy menstrual bleeding' is 2,8- i.e. a disproportionality.
- Regulatory Context: The broad clinical issue of "menstrual disorders" was reviewed in the 9th MSSR for Comirnaty.

A signal is being sent in parallell for mRNA-vaccine Spikevax.

Comment PRAC Rapporteur:

The signalling Member State stated that NoMA has fully processed 787 cases belonging to the PT 'heavy menstrual bleeding' as of 3 Jan 2022. However, currently no details are available, which precludes full appraisal of prioritization of this signal.

Further details regarding NCA's assessment of the fully processed 787 Norwegian cases would be highly appreciated. The signalling Member State is requested to provide further details if available, in particular focusing on the serious and well-documented/medically confirmed cases, and provide for the all cases a clear breakdown of number of cases that were:

- Medically confirmed.
- Supportive of causality (by WHO scaling).
- Unassessable.
- Unsupportive of causality due to presence or other causes, risk factors, underlying conditions, confounding medication.
- Details of co-reported AEs (if any) that may confound the menstrual changes.
- Exclude (or stratify) cases in which women used hormonal contraception (including hormonal IUDs), as these women have no natural menstrual period, but hormonally induced withdrawal bleedings.
- Exclude (or stratify) patients with an iron IUD as in these women the natural menstrual pattern is influenced by the presence of iron.

- Stratify patients that received heterologous primary or booster schemes [as this is particularly relevant within the NO context].

Depending on the results further regulatory action can be considered, as appropriate.

Note that a similar review of nationally reported cases is ongoing in the Netherlands.

Signal description

Spontaneous reports:

As the majority of the ICSRs on the issue of menstrual disturbances are reported and/or classified as non- serious, there is a huge backlog of uncoded/unhandled cases in Norway and most likely in other European countries.

However, per 12 JAN 2022, for both mRNA-vaccines NoMA has fully processed over 3400 ICSRs belonging to the SOC "Reproductive system and breast disorders" whereof 2800 cases belonging to the HLGT "Menstrual cycle and uterine bleeding disorders" which have been submitted to EudraVigilance.

NoMA has fully processed 787 cases belonging to the PT 'heavy menstrual bleeding' as of 3 JAN 22, but our back log is significant.

It is interesting to note that LAREB (the Netherlands pharmacovigilance centre) who currently has no back log has registered 3533 ICSRs coded with the PT heavy menstrual bleeding related to Comirnaty in their report dated 22.12.21 [3].

Comment PRAC Rapporteur:

Further details regarding NCA's assessment of the fully processed 787 Norwegian cases would be highly appreciated (See previous comment).

Note that the PRAC Rapporteur concluded that further evaluation is warranted, but at the moment the available evidence regarding a causal relation between COVID-19 vaccination and heavy menstrual bleeding, amenorrhoea, and post menopausal bleeding is possible, but inconclusive.

Positive rechallence cases:

NoMA has registered approximately 100 cases of women experiencing changes in menstrual cycle or bleeding pattern after both the first and second dose of an mRNA-vaccine (including mix-and-match vaccine schedule). These are indicative of a link between reactions related to menstrual cycle and mRNA vaccines. A list of cases could be provided to the PRAC-Rapporteurs on request.

Below are two examples:

Example 1: This is a patient report from an adult female. She was vaccinated with her second dose of Comirnaty. The patient states: "Constant bleed after dose 1, lasting several months, significant amounts. Increased menstrual pain and more bleedings reoccured after dose 2."

Example 2: This is a health care professional report from a GP. The report concerns an adult female who according to the GP had menstrual disturbances after the first dose of Comirnaty. The condition worsened after the second and third dose. Her bleeding periods are prolonged, and the interval has

been shortened. She now bleeds for up to 3 weeks; her bleedings are more severe, and she has more pain than she used to. Her menstrual cycle is usually regular.

Comment PRAC Rapporteur:

The selection criteria for presenting these two examples is not entirely clear. Although causality is possible based on the reported positive rechallenge, essential information is missing, precluding in-depth assessment. For instance, in both cases information regarding time-to-onset, medical history, underlying conditions, confounding factors, co-medication (*e.g.* hormonal contraceptives), SARS-CoV-2 status should be carefully considered.

It is understood that the approximately 100 cases of positive rechallenge were reported for all menstrual cycle or bleeding pattern changes, hence not specifically for the PT heavy menstrual bleeding exclusively.

A clear breakdown of number of cases should be provided of:

- Reports of positive rechallenges of PT heavy menstrual bleeding.
- Reports of positive rechallenges of other specific menstrual changes PTs andif applicable, details of other co-reported AEs.
- Reports of negative rechallenges, *i.e.* post-dose 1 only which are considered unsupportive for causality.
- Reports for which rechallenge information was non-informative, *i.e.* AEs post-1st dose had not resolved at the time of the administration of the 2nd dose.
- Reports which were insufficiently documented / unclassifiable.

Population cohort studies:

There is an increase in the incidence of menstrual changes among young women after vaccination against coronavirus, according to initial findings from population studies by the Norwegian Institute of Public Health (N = 6000, age 18- 30 years).

Even though the study does not address heavy menstrual bleeding specifically, it provides evidence of a causal association. This evidence was not available at time of review in the MSSR. (4)

Comment PRAC Rapporteur:

Although these first findings in this Norwegian study (not peer-reviewed yet), warrant further evaluation, NO's conclusion that the cited Norwegian study *"provides evidence of a causal association between the COVID-19 vaccines and women's menstrual cycle"* is currently not endorsed.

Within the EU and global context reports of menstrual disorders following COVID-19 vaccination have already been identified for all COVID-19 vaccines and are currently being closely monitored through routine pharmacovigilance (*i.e.* routine signal/trend analysis, monthly summary safety reports and periodic safety update reports).

At this moment the PRAC considers that based on the currently available evidence, it cannot be concluded that COVID vaccination causes menstrual disorders.

The current evidence includes clinical trial data, the spontaneous reports in Eudravigilance (which includes the NL cases) and published scientific literature including the recently published initial findings

from population studies by the Norwegian Institute of Public Health, which reported an increase in the incidence of menstrual changes among young women after vaccination against coronavirus:

Menstrual changes following COVID-19 vaccination - NIPH (fhi.no)

Increased incidence of menstrual changes among young women after coronavirus vaccination - NIPH (fhi.no)

The main purpose of the Norwegian study was to clarify whether bleeding disorders occur more frequently in vaccinated women than in non-vaccinated women.

The study based on 4000 women shows that there is an increased incidence of menstrual disorders in young women age 18- 30 after they were vaccinated against Covid (mRNA vaccines).

The MS1 Medicines Agency by mid November 2021 assessed all the adverse event reports of menstrual disorder and COVID-19-vaccinations that the agency had received by then (around 3900 reports from women in total). Based on the analysis of these reports, the MS1 Medicines Agency did not find evidence to support the theory that COVID-19-vaccines trigger menstrual disorders.

The authors of the Norwegian study currently do not draw any conclusion regarding a causal role of the vaccination. As has been indicated by the authors, the results of this study should be interpreted cautiously, due to the following:

- Study design, *i.e.* self-reported outcomes obtained through a survey/questionnaire, which may pose a risk on subjectivity and reporting and recall bias.
- High incidence of menstrual cycle changes at baseline.
- Confounding by pre-vaccination anxiety-/lockdown stress, undetected (corona)infections cannot be fully excluded at this moment.

There was a generally high incidence of the various menstrual disturbances among menstruating women aged 18–30 years: As many as 37.8% reported at least one change during their last period before vaccination. After the first dose, 39.4% reported at least one change, and after the second dose, 40.9%.

Specified by symptoms, during the last cycle before the 1st vaccination dose 7-18% of the participants already reported a menstrual change (relative to their normal cycle).

After vaccination this percentage appears increased for some specific symptoms, i.e. heavier than normal 7.6 *vs* 13.6%, but overall there does not appear to be a great difference in ranges: 7.6-18.3% *vs.* 10.9-15.8%, before and after the 1st dose, respectively.

In summary, from these study results no causal relation between COVID-19 vaccination and menstrual cycle changes can be established.

The authors' word of caution is agreed that: *Menstrual changes are very common among women of childbearing age and can have various causes. Menstruation can be affected by many factors, such as infections, medicines, hormones / contraception, fibroids, endometriosis or other diseases of the uterus and cervix. When many women are vaccinated, it is therefore expected that some will experience menstrual changes and unexpected bleeding around the time of vaccination by coincidence.*

Examples of cases of heavy menstrual bleedings

Case 1: This case is a health care professional report of a girl experiencing a life- threatening vaginal bleed. The girl was vaccinated with Comirnaty. She had her first period 12 days later, but the bleeding did not subside, and she was admitted to hospital for immediate help on 14 days after having her first period with severe bleeding anemia. The patient had hemoglobin of 4.0 g/dL and received four blood transfusions and three bags of fresh frozen plasma. She has been examined for coagulation disorders with completely normal findings. This includes INR, vWf, APTT, fibrinogen, coagulation factor IX, VII, VIII. The patient is previously healthy. Does not use medication. Ultrasound showed blood in the uterus and thick and even mucous membrane. CT abdomen showed the same findings. The patient's outcome was recovered/resolved.

We have one additional report of a girl requiring blood transfusion due to a prolonged menstrual bleeding, reported by a parent.

Case 2: This is a serious health care professional report with a positive rechallenge of bleedings and hospitalisations. An adult woman experienced heavy vaginal bleeding 2 days after her first dose of Comirnaty. The bleeding was much heavier than a normal menstruation and would not stop. She was admitted to hospital 8 days later for uterine scraping and blood transfusion. 17 days after the first dose of Comirnaty the patient informs that the situation had stabilized, but the bleeding had still not stopped completely.

42 days after her first dose of Comirnaty she received the second dose of Comirnaty, and she was again admitted to hospital with heavy vaginal bleeding that resulted in uterine scraping and blood transfusion. The time for admission the second time is reported as the month when she received the second dose of Comirnaty, so exact date is not known, but is within eight days from vaccination. The bleeding stopped the last week of the next month following the 2nd dose vaccination month, and her menstrual cycle is seemingly back to normal.

Case 3: This is a health care professional report from a physician, concerning an adult woman who was hospitalised due to severe bleedings. She was vaccinated with Comirnaty, third dose. She experienced a menstrual bleeding starting two days after the vaccination. She was unsure whether her period was due then. She uses a contraceptive implant since this summer. Has since then had an irregular menstruation. Initially once per month, then more frequently than once per month. The amount of blood was not more than normal. She then travelled abroad 9 days after receiving the third dose of Comirnaty and was admitted to hospital due to persistent bleeding. Ultrasound reportedly found thin mucous membrane in the uterus. She started treatment with progestogen 1 mg for eight days, without effect. She has previously only experienced irregular bleedings relating to change of contraceptives. She has frequent heavy menstrual bleeding during the day and night. Stomach pain all the time. Uses paracetamol 1 gram several times a day, without effect.

Weight reduction of 2 kg during the last four weeks. Feels healthy. She performs sustained physical exercise every day. As concomitant medication, the patient is treated with budesonide since 10 days after receiving third dose of Comirnaty for Crohns disease. Uses Acetylic salicylic acid 75 mg daily. Medical history includes an aortic valve replacement. Her menstrual bleeding was not recovered at time of report, 32 days after the third dose of Comirnaty and she has been bleeding for 4 weeks.

Case 4: This is a health care professional report concerning an adult woman who was hospitalised due to a severe bleeding. She has had two pregnancies previously (gravida 2, para 2). Her menstrual cycle is usually regular, lasting 3-4 days. Last menstruation in the month of first vaccination with Comirnaty. She has not had similar heavy menstrual bleedings before. She was vaccinated with Comirnaty. Two days after she had a severe vaginal bleeding, fresh blood with clots. No pain. Somewhat heavy breathing, but no dizziness. Hb 6.7 at admission, requiring blood transfusion of 2 units of salt-adenin-glucose (SAG). Hb 8.9 13 days after vaccination with Comirnaty. Not suspected polyp or myoma. She was treated with tranexamic acid, nortetisterone and given iron supplementation. Primary suspected cause is anovulatory bleeding. Histology results from a biopsy taken from the uterus shows: Endometrium in a prolonged proliferation phase with focal eosinophil and papillary metaplasia, not atypical (premenopausal endometrium).

Case 5: This serious report concerns a 20–30-year-old female with heavy menstrual bleeding starting 6 hours after second vaccination with the Pfizer/BioNTech vaccine. The menstrual bleeding had to be stopped with medication (blood thickers). Patient has an IUD for 9 years now and never had a menstruation in all those years. Patient has factor VII deficiency and bleeding is very dangerous for her because of her condition. Now after both the first and the second vaccination she had a very severe menstrual bleeding, despite the IUD. No further diagnostics are performed. No other concomitant medication. Patient did not have a covid-19 infection prior to vaccination. BMI is high.

Case 6: This is a patient report concerning an adult female patient who had a hysterectomy due to prolonged/severe bleedings. She was vaccinated with Comirnaty, first dose. The patient reports of bleedings, starting second day after first dose and persisting, except for a few days off. The bleedings were severe and led to hospitalisations. She has been treated with "blood stopping agents", with and without effect. Last hospitalisation is approx. 3 months after first dose of Comirnaty. A hysterectomy was performed on approx. 3,5 months after first dose of Comirnaty.

Comment PRAC Rapporteur:

Case 1: Causality is possible based on the TTO of 13 days, and exclusion of underlying coagulation disorders. However information regarding other possible confounders (*e.g.* (asymptomatic) SARS-COV-2 infection) is lacking.

The additional case mentioned under **Case 1** is insufficiently documented to allow causality assessment.

Moreover, it is not clear whether these 2 girls are already having previous regular menstrual bleeding. When the menstrual bleeding has only recently started, it is generally not regular yet.

Case 2: Causality is possible based on TTO and positive rechallenge, however it is not documented whether alternative etiologies have been systematically excluded.

Case 3: Heavy bleeding only occurred following the 3rd dose and not following the 1st and 2nd dose, which is not supportive for a causal relation. The use of hormonal contraception (including hormonal IUDs) precludes causality assessment as these women have no natural menstrual period, but hormonally induced withdrawal bleedings.

Case 4: Causality cannot be ruled out due to TTO of two days. However considering the patient's age and histology results - Endometrium in a prolonged proliferation phase with focal eosinophil and papillary metaplasia, not atypical (premenopausal endometrium) - may suggest early menopausal transition as a plausible alternative cause.

Case 5: This case is not assessable as the patient has a clotting disorder (factor VII deficiency) and very likely uses a hormonal IUD. An iron IUD is not suitable in a patient with a clotting disorder, as iron IUDs increase the amount of menstrual bleeding.

Case 6: Causality cannot be ruled out based on short TTO of 1 day, but details regarding diagnostic work-up, comedication, medical history, exclusion of alternative etiologies is lacking.

In summary, based on assessment of the 6 selected reasonably well-documented cases causality between vaccination and heavy menstrual bleeding cannot be ruled out in 3 out 6 cases (cases 1, 2, 6).

Cases 3 and 5 are not assessable due to hormonal contraceptive use and an underlying clotting disorder. In case 4, a likely alternative cause has been diagnosed.

In none of the cases information regarding preceding SARS-CoV-2 infection (including asymptomatic) has been provided.

It seems that this selection of patients is not random and therefore prone to bias. It needs to clarified on which grounds and for which purpose these cases were extracted from the dataset and discussed separately. In order to allow in-depth assessment of a causal relation between COVID-19 vaccination and heavy menstrual bleeding further detail of all cases is required (see previous comments).

Publications:

In a retrospective cross-sectional study by Li *et al.* [5] laboratory and clinical data from hospitalised women of child-bearing age diagnosed with COVID-19 were analysed. Menstrual data from 177 women were analysed. The authors conclude that the average sex hormone concentrations and ovarian reserve did not change significantly. Nearly one-fifth of patients exhibited a menstrual volume decrease or cycle prolongation. The authors propose that the menstruation changes of these patients might be the consequence of transient sex hormone changes caused by suppression of ovarian function that quickly resume after recovery. It should be noted that the patients were followed up, and 84% returned to a normal menstrual volume and 99% returned to their normal cycle within 1-2 months of discharge, suggesting that changes in menstruation caused by covid-19 were most likely temporary changes and resolved in a short period. One 40-49-year-old patient indicated in the follow-up that she had stopped menstruating for 4 months after COVID-19 onset and had excluded pregnancy as a cause, but considering that she was within her perimenopausal period, they believed that the observation time of menstruation should be extended in her case.

Comment PRAC Rapporteur:

The finding that changes in menstruation can be caused by COVID-19 infection, underscores the importance to carefully consider and exclude preceding SARS-CoV-2 infection (including asymptomatic) as confounder or effect modifier.

Recommendation:

The MAH should review data from clinical trials and post marketing data, including:

- Provide an overview of the age of the female study participants in the reactogenicity subgroup of the clinical study, including median age, and provide the number of women of childbearing potential the study included.

- Perform a follow up with all female participants of childbearing age in the clinical trial to investigate for any reaction related to their menstruation and ovulation/fertility, including pregnancy and pregnancy outcome.
- Analyse a number of post marketing reports to investigate when the time of vaccination took place relating to the time of ovulation, the luteal phase and so on, in those ICSRs where the information of the menstrual cycle is known, to see if there might be a pattern.

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4. https://www.fhi.no/en/news/2021/menstrual-changes-following-covid-19-vaccination/
5. Li K, Chen G, Hou H, Liao Q, Chen J, Bai H, Lee S, Wang C, Li H, Cheng L, Ai J. Analysis of sex hormones and menstruation in COVID-19 women of child-bearing age. Reprod Biomed Online. 2021 Jan;42(1):260-267. doi: 10.1016/j.rbmo.2020.09.020. Epub 2020 Sep 29. PMID: 33288478; PMCID: PMC7522626.

2.2. Signal confirmation

Overall, a total of 16,422 ICSRs reporting heavy menstrual bleeding following tozinameran are reported in EudraVigilance (eRMR cut-off 23 Jan 2022).

It is acknowledged that the absolute number of spontaneously reported cases is high, but this not unexpected taking into account the high background incidence of menstrual disorders irrespective of vaccination, and the pandemic context with an unprecedented high number of administered doses of vaccines, and the large (social) media attention on this topic.

Spontaneous reporting rates should be interpreted cautiously, as both underreporting and stimulated reporting cannot be excluded.

Based on NO and MS11 national reviews some supportive cases have been identified in which a causal relation cannot be ruled out based on compatible TTO, positive rechallenge information and absence of alternative causes. However, with such large numbers of vaccinees, chance findings cannot be excluded either.

In the vast majority of the MS11 cases essential information is lacking and further in-depth evaluation of the signal by the MAH is warranted.

Further details regarding NCA's assessment of the fully processed 787 Norwegian cases would be highly appreciated. The signalling Member State is requested to provide further details if available, in particular focusing on the serious and well-documented/medically confirmed cases, and provide for the

all cases a clear breakdown of number of cases that were:

- Medically confirmed.
- Supportive of causality (by WHO scaling).
- Unassessable.
- Unsupportive of causality due to presence or other causes, risk factors, underlying conditions, confounding medication.
- Details of co-reported AEs (if any) that may confound the menstrual changes.
- Exclude (or stratify) cases in which women used hormonal contraception (including hormonal IUDs), as these women have no natural menstrual period, but hormonally induced withdrawal bleedings.
- Exclude (or stratify) patients with an iron IUD as in these women the natural menstrual pattern is influenced by the presence of iron.
- Stratify patients that received heterologous primary or booster schemes as this is particularly relevant within the NO context.

Depending on the results further regulatory action can be considered, as appropriate.

Note that similar review of nationally reported cases is ongoing in the Netherlands.

Nevertheless, the signal is considered weak based on the following:

- In the pivotal randomized clinical trial for Comirnaty the number of observed menstrual cycle abnormalities adverse events was balanced between placebo and active arms. The PT Heavy menstrual bleeding was not reported specifically in the study.
- Within the context of an exposure of 545 million administered doses in the EU/EEA countries (status 02 Jan 2022), the number of supportive cases is considered limited.
- Although heavy menstrual bleeding is disproportionally reported in EV, it is very difficult to assess whether the observed number of cases exceeds the expected number of cases, due to the high incidence of the AE at baseline.
- Confounding by pre-vaccination anxiety-/lockdown stress, undetected (corona)infections cannot be fully excluded at this moment.
- Although there may be a potentially plausible mechanism, a coincidental finding cannot be excluded either at this moment.

Therefore, a default 60/60 time table is considered proportional, also considering the type/volume of data to be assessed.

2.3. Proposed recommendation

Within 60 days following receipt of this report the MAH is requested to submit a cumulative review of all cases concerning Comirnaty associated heavy menstrual bleeding from all sources, including any relevant articles from literature and to discuss probable mechanism(s) of action for the occurrence of vaccine-associated heavy menstrual bleeding following administration of Comirnaty.

The MAH should review data from clinical trials, literature and post marketing data, including:

- Provide an overview of the age of the female study participants in the reactogenicity subgroup of the clinical study, including median age, and provide the number of women of childbearing potential the study included.
- Perform a follow up with all female participants of childbearing age in the clinical trial to investigate for any reaction related to their menstruation and ovulation/fertility, including pregnancy and pregnancy outcome.
- Analyse a number of post marketing reports to investigate when the time of vaccination took place relating to the time of ovulation, the luteal phase and so on, in those ICSRs where the information of the menstrual cycle is known, to see if there might be a pattern.

Focus of the review should be on the serious and well-documented/medically confirmed cases, and the MAH should provide for the all cases a clear breakdown of number of cases that were:

- Medically confirmed.
- Supportive of causality (by WHO scaling).
- Unassessable.
- Unsupportive of causality due to presence or other causes, risk factors, underlying conditions, confounding medication.
- Details of co-reported AEs (if any) that may confound the menstrual changes.
- Exclude (or stratify) cases in which women used hormonal contraception (including hormonal IUDs), as these women have no natural menstrual period, but hormonally induced withdrawal bleedings.
- Exclude (or stratify) patients with an iron IUD as in these women the natural menstrual pattern is influenced by the presence of iron.
- Stratify patients that received heterologous primary or booster schemes [as this is particularly relevant within the NO context].

The MAH should discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for changes to the relevant sections within this discussion.

The procedure should follow a 60/60 day Time Table considering the type/volume of data to be assessed.

Of note, the same signal has been confirmed for Spikevax and it is proposed to align the final PRAC recommendation during the PRAC plenary meeting of 7-10 February 2022.

2.4. Adopted PRAC recommendation

Having considered the available evidence from national reviews (post marketing cases and published studies), the PRAC has agreed that the MAH for COVID-19 mRNA Vaccine Comirnaty (BioNTech Manufacturing GmbH) should perform a cumulative review of all cases of heavy menstrual bleeding

from all sources, including, but not limited to, available data from clinical trials, literature and post marketing exposure. The MAH should provide by 7 April 2022 answers to the below List of Questions concerning clinical trials, literature, case overview and review, possible mechanism of action and exposure in females of childbearing potential.

1. Clinical trials

The MAH should provide an overview and clinical evaluation of cases of heavy menstrual bleeding, reported during pivotal clinical trials. The clinical evaluation should include age, childbearing potential, reported risk factors for heavy menstrual bleeding, concomitant medication, patient medical history including previous menstruation pattern, duration of the event and outcome. This information should be considered in the context of the total number of females, including of childbearing potential participating in the study.

The MAH should clarify how adverse events related to heavy menstrual bleeding were reported, i.e. if these were solicited adverse events or spontaneously reported by the participants.

2. Published literature

The MAH should perform a literature review on the possible association between heavy menstrual bleeding and COVID-19 mRNA vaccine Comirnaty. The literature review should include, but not be limited to a discussion on the studies by: Lill Trogstad et al.1, Nguyen et al.2 and Edelman et al.3.

3. Case overview

The MAH should list the number of reported cases of the preferred term heavy menstrual bleeding stratified by:

- worldwide and region;
- country in the EU/EEA;
- dose number in series;
- seriousness;
- reporter (medically/non-medically confirmed);
- positive rechallenge.

4. Case review

The case review should prioritise serious and/or medically confirmed cases, where information on risk factors and medical history is included. Special focus should be given to cases in which the previous menstruation pattern is known, and to cases of heavy menstrual bleeding with positive rechallenge.

[1] Trogstad, Lill, Increased Occurrence of Menstrual Disturbances in 18- to 30-Year-Old Women after COVID-19 Vaccination (January 1, 2022). Available at SSRN: https://ssrn.com/abstract=3998180 or http://dx.doi.org/10.2139/ssrn.3998180

[2] Nguyen BT, Pang RD, Nelson AL, Pearson JT, Benhar Noccioli E, Reissner HR, et al. (2021) Detecting variations in ovulation and menstruation during the COVID-19 pandemic, using real-world mobile app data. PLoS ONE 16(10): e0258314. https://doi.org/10.1371/journal.pone.0258314

[3] Edelman A, Boniface ER, Benhar E, Han L, Matteson KA, Favaro C, Pearson JT, Darney BG. Association Between Menstrual Cycle Length and Coronavirus Disease 2019 (COVID-19) Vaccination: A U.S. Cohort. Obstet Gynecol. 2022 Jan 5. doi: 10.1097/AOG.0000000000004695. Epub ahead of print. PMID: 34991109

The case review should include a WHO-UMC Causality assessment, and a justification of causality category should be given for each case. The MAH should provide for all cases a clear breakdown of the number of cases that were either supportive of causality/ unsupportive due to presence of other causes, risk factors, underlying conditions, confounding medication/ unassessable.

The following information should be stratified:

- Details of medically relevant co-reported adverse events (if any);
- Cases in which women used hormonal contraception (including hormonal intrauterine devices);
- Cases with other types of intrauterine devices;
- Cases that received heterologous primary or booster schemes.

If available, the MAH should provide information on when vaccination took place relating to the time of ovulation, the luteal phase and so on, in those ICSRs where the information on the menstrual cycle is known and discuss whether a pattern might exist.

When excluding cases from the review, a justification for doing so should be provided by the MAH.

Based on a review of case reports with inconclusive causality due to confounding factors and/or lacking information, the MAH should provide a nuanced discussion of whether Comirnaty may have aggravated the condition in cases where causality cannot be firmly established.

5. Mechanism of action

The MAH should discuss the pathophysiology of heavy menstrual bleeding and whether any biological plausibility/mechanism of action exists.

6. Exposure in females of childbearing potential

The MAH should provide an estimation of the number of women of childbearing age that have been vaccinated with Comirnaty.

The MAH should discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for changes to the relevant sections within this discussion.

The PRAC will assess the cumulative review within a 60 days' timetable.

3. Additional evidence

3.1. Assessment of additional data

3.1.1. Supplementary information from Trogstad et.al.

During the assessment of the signal, the Norwegian Medicines Agency received unpublished data from Trogstad et.al. with supplementary analysis from the study "Trogstad, L. Increased Occurrence of Menstrual Disturbances in 18- to 30-Year-Old Women after COVID-19 Vaccination" which has been discussed in the assessment of the MAH's response.

The respective analysis is available as a preprint at:
https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4324853

Reported menstrual changes from heterologous primary vaccination

PRAC Rapporteur's comment

The assessment of these supplementary analysis is included in the PRAC Rapporteurs assessment of the MAHs discussion of the study by Trogstad et.al. later in this assessment report

3.1.2. Supplementary information from Caspersen et.al

PRAC Rapp Comment: This study was not published when it was made available to the PRAC Rapporteur on May 6, 2022. This study is now published: https://pubmed.ncbi.nlm.nih.gov/36517325/

PRAC Rapporteur's comment

The study by Caspersen et al. from the Norwegian Institute of Public Health studied the occurrence of menstrual disturbances in adolescents (12-15 years) following one dose of Comirnaty. The authors have submitted a manuscript that is not yet peer-reviewed or published as a pre-print. Thus, this information must be read in that context and treated as confidential.

Participants were part of an ongoing cohort (MoBA) established many years previously. There were 19,310 respondents (response rate 64%). Boys (9,947), non-menstruating girls (1,646), those registered with >1 dose of COVID-19 vaccine (144) and those who had received vaccine before August 1, 2021 (8) were excluded, and the remaining 1,466 subjects were included in the analysis.

Information regarding vaccination status and COVID-19 disease was double-checked with records in national registries. The study applied a self-controlled case series design (SCCS), which adjusts for most confounding factors. Further, the questionnaire included several topics not related to menstruation to be answered prior to the menstrual disorders-questions to exclude awareness of these disturbances as a primary incentive to respond.

The study showed that the occurrence of heavier bleeding after vaccination was significantly higher than that of the most recent menstruation prior to vaccination (relative risk: 1.61, 95% CI: 1.43 to 1.81). While menstruation disorders were overall common also in the unvaccinated group (22.3%), an increase was noted in the vaccinated group in the first cycle after vaccine (from 22.6% to 25.1%). Reports of heavy menstrual bleeding showed the largest relative increase in this group (4.7% to 7.3%), other events did not show any change (longer interval, spot bleeding, period pains).

The study has some limitations, one being that questionnaires were answered by the mothers on behalf of their daughters. Questions regarding menstruation both before and after vaccination were answered in the same questionnaire at one time-point. Median time between vaccination and completion of the survey was 27 days, which had the advantage of reducing recall bias, but led to exclusion of subjects where no information regarding menstrual disorders could be obtained. Not all participants in the cohort opted to answer the questionnaire and some selection bias cannot be ruled out. Not all items related to menstrual disorders showed a change after vaccination, indicating that participants were not overall biased against menstrual cycle changes.

In conclusion, despite some limitations, the results of the study point to an increased risk of heavy menstrual bleeding after vaccination with one dose of Comirnaty in girls aged 12–15 years. This is consistent with findings in the older age group 18–30. This consistency supports an association between heavy menstrual bleeding and COVID-19 mRNA vaccination.

3.1.3. Assessment of response

Question 1 – Clinical Trials

MAH's response:

There were 12 cases of heavy menstrual bleeding (unsolicited reports).

These 12 were from the trials C4591001 and C4591031.

- 3 of the 12 events occurred after placebo
- 9 of the 12 events occurred after receipt of active study vaccine.

In the placebo-controlled portion of the C4591001 study, prior to treatment assignment unblinding, there were 6 events of heavy menstrual bleeding; 4 of these events were after receipt of active vaccination and 2 events after receipt of placebo.

The MAH have provided an overview of the 4 cases that received active vaccine: all resolved with no sequelae, mean age was 35.5 and mean time to onset was 39.8 days (range 3 – 114 days). Mean duration was 78.3 days (range 6 – 151 days).

Across both studies, in the placebo-controlled portions, in the 3 events after placebo-vaccine; mean duration was 53.3 days, range 5 – 142 days.

The MAH describes five cases with pre-existing medical history which may be relevant. 2 had pre-existing history of menorrhagia (1 following placebo, 1 following active vaccine), 2 participants with history of previous gynaecological surgery (both following active vaccine) and 1 with history of thrombophilia (following placebo). It is also mentioned one participant reported having a Mirena (hormonal) intrauterine device.

PRAC Rapporteur's comment

As a general note, the overview/description provided by the MAH is unstructured, and it is difficult to make the figures from the detailed description of the events add up to the total number of 12 events as stated initially by the MAH.

The MAH disregards/does not discuss the numerical imbalance of the clinical trials – 9 (vaccine) vs 3 (placebo), and the imbalance 4 (vaccine) vs 2 (placebo) in the placebo-controlled portion of the C4591001 study.

During confirmation of the signal, data from the pivotal randomized clinical trial for Comirnaty, C4591001 was discussed, showing that the number of observed menstrual cycle abnormalities adverse events were balanced between placebo and active arms:

"During the placebo-controlled follow-up, adverse events coding to the HLGT Menstrual cycle and uterine bleeding disorders were reported for 12 participants in the BNT162b2 group and for 13 participants in the placebo group, corresponding to IRs of 0.14 per 100 PY and 0.16 per 100 PY, respectively (Table 1). These results show very low incidence and no imbalance in reporting incidence between the BNT162b2 and placebo groups."

These figures were on HLGT-level and not specific for the PT heavy menstrual bleeding. It is therefore important to acknowledge that when looking at a specific PT, the numbers are imbalanced.

The MAH has not responded adequately to the request "This information should be considered in the context of the total number of females, including of childbearing potential participating in the study."

The purpose behind this question was to investigate whether the proportion of females of childbearing potential in the trial is representable of the post marketing population, or whether the trial was overly represented by women not of childbearing potential. Such an important issue should have been correctly addressed.

Range of bleeding time was from 6 – 151 days, which means that one participant bled for 151 days. The MAH has not provided details on this case. Such details were not specifically requested but would have been helpful for assessment. Also, there seem to be inconsistencies in the numbers provided by the MAH, because no cases in the line listings provided (Appendix 1 and 2) have a duration of 151 days.

Regarding the discussion of pre-existing medical history: In the trial of such a size (23 789 female participants), one can assume that risk factors have been evenly distributed in the study population, hence the discussion on pre-existing medical history is less relevant. On the contrary, it could be discussed in terms of contributing risk factors.

Question 2 - Published literature

The MAH should perform a literature review on the possible association between heavy menstrual bleeding and COVID-19 mRNA vaccine Comirnaty. The literature review should include, but not be limited to a discussion on the studies by: Lill Trogstad et al., Nguyen et al. and Edelman et al.

MAH's response:

The MAH included 7 publications on the topic: Trogstad et al., Nguyen et al., Edelman et al., report from LAREB, weekly summary from the MHRA Yellow Card Reporting, Lee et al., Male et al., and Alvergne et al.

The publications included by the MAH were the following:

Lee K, Junkins E, Luo C, et al. Investigating trends in those who experience menstrual bleeding changes after SARS-CoV-2 vaccination. Available February 11, 2022.

MAH's response:

The MAH does not provide a description/overview of the study (such as its design and number of participants). The MAH refers to this publication and states that in this sample, of currently and formerly menstruating people in the US, 42% of people with regular menstrual cycles bled more heavily than usual while 44% reported no change after being vaccinated. Among respondents who typically do not menstruate, 71% of people on long-acting reversible contraceptives, 39% of people on gender-affirming hormones and 66% of post-menopausal people reported breakthrough bleeding. Increased/breakthrough bleeding was significantly associated with older age, systemic vaccine side effects (fever, fatigue), history of pregnancy or birth, and Hispanic/Latinx ethnicity. The MAH states that interestingly, the authors also examined the relationship of specific reproductive conditions often associated with altered menstrual bleeding by comparing respondents with diagnosed conditions to respondents with no reported reproductive conditions. A higher proportion of respondents with endometriosis (51.1%), menorrhagia (44.3%), fibroids (49.1%), PCOS (46.2%), and adenomyosis (54.9%) reported experiencing a heavier menstrual flow post-vaccine than the respondents without diagnosed reproductive conditions (40.9%).

The MAH states that this study has several limitations, with the main ones being participation bias and the lack of a comparator group.

PRAC Rapporteur's comment

This is a retrospective survey-based study with 39,129 respondents, between 18 and 80 years of age. All participants were fully vaccinated and had not contracted COVID-19 (diagnosed or suspected). 21,620 were vaccinated with Comirnaty.

This is a large survey, but as is stated by the authors it cannot estimate prevalence or incidence based on the methodological approach, and the associations reported cannot establish causality. The authors state that their results highlight that many people noted changes in their menstrual bleeding, with 56% of the regularly menstruating sample reporting some change in their menstrual bleeding after one or more of the vaccine doses.

The MAH's review focuses for the most part on the analysis of a subgroup (respondent with diagnosed conditions). As they account for a mere 13% (n = 5000) of the participants, the MAH's approach is questioned.

Most participants in the study (87%) reporting menstrual changes did not have these medical conditions. However, the Rapporteur agrees with the MAH that the higher reported incidences in these patients are interesting, but from another perspective. The findings might indicate that some of these conditions predispose the woman to an alteration of her menstrual cycle. This is important to remember, since ICSRs submitted on these individuals could be at risk of being dismissed as confounded. Please see comments and discussion related to the case review.

The MAH states that the study has several limitations, with the main ones being participation bias and the lack of a comparator group which is agreed upon.

However, the authors addressed their research questions according to the design of the study, seeking to overcome such limitations in order to increase validity of the findings:
- 1) What is the range of menstrual bleeding changes reported by regularly menstruating respondents after being administered the SARS-CoV-2 vaccine?
-2) To what extent are non-menstruating respondents reporting breakthrough bleeding after being administered the SARS-CoV-2 vaccine?
3) Are there trends among those with a changed bleeding pattern to help determine proximate mechanisms acting on the uterus?

These questions are of a descriptive character. Further, each study participant is considered as its own control, as outcome is registered before/after vaccination. Regarding recruitment to the study, the authors sought to include a wide array of patients. It is acknowledged that experiencing menstrual disorders following vaccination may have served as an incentive. However, the authors have succeeded in enrolling women experiencing no changes. The MAH's arguments regarding participation bias and lack of control group are acknowledged. However, the MAH's dismissal of the conclusions of the study in its entirety is not endorsed, as we consider the results provide some information.

Edelman – Edelman A, Boniface ER, Benhar E, et al. Association Between Menstrual Cycle Length and Coronavirus Disease 2019 (COVID-19) Vaccination: A U.S. Cohort [published online ahead of print, 2022 Jan 5]. Obstet Gynecol.

MAH's response:

This study was specifically requested in the LoQ. However, the MAH's description of the publication is one sentence in section 2.7 Summary and Conclusion: "A well-designed US study of self-reported menstrual cycle data by Alison Edelman et al. did not support a significant effect of vaccination on the number of days of menstrual bleeding."

PRAC Rapporteur's comment

The review presented by the MAH is scarce, and the results are not discussed in detail, which was expected.

The study analysed prospectively tracked menstrual cycle data using a smart phone application. The study included U.S. residents aged 18 -45 years, with normal cycle length (24 – 38 days) for three consecutive cycles over a corresponding time-period. The study included 3,959 individuals (vaccinated 2,402 and unvaccinated 1,556), of which 55% received Comirnaty. The authors calculated the mean within-individual change in cycle and menses length (three pre-vaccine cycles vs first- and second-dose cycles in the vaccinated cohort, and the first three cycles vs cycles four and five in the unvaccinated cohort). Overall, COVID-19 vaccine was associated with a significant increase in cycle length, that was less than 1-day for both vaccine-dose cycles compared with pre-vaccine cycles (first dose 0.71 day-increase, 98.75% CI 0.47-0.94; second dose 0.91, 98.75% CI 0.63-1.19); unvaccinated individuals saw no significant change compared with three baseline cycles (cycle four 0.07, 98.75% CI -0.22 to 0.35; cycle five 0.12, 98.75% CI -0.15 to 0.39). In adjusted models, the difference in change in cycle length between the vaccinated and unvaccinated cohorts was less than 1 day for both doses (difference in change: first dose 0.64 days, 98.75% CI 0.27-1.01; second dose 0.79 days, 98.75% CI 0.40-1.18).

The vaccinated cohort was slightly older (34% 30–34 years of age vs 24% among unvaccinated) and more likely to be nulliparous (79% vs 69%) and college educated (77% vs 60%) as compared with the unvaccinated group.

This study is strengthened by the control group and is of a moderate size. An important limitation is that vaccinated and unvaccinated women potentially differs in various aspects indicated by the difference in age, education and parity. However, the findings may indicate an association between COVID-19 vaccines and slightly increased cycle length. The clinical implications of an increase this magnitude are less clear and may be considered as negligible. However, there is a sub-population that is more affected. The increase in cycle length for both the first and second vaccine cycles appears to be driven largely by the 358 individuals who received both vaccine doses within a single cycle (cycle four). This subgroup experienced a 2-day unadjusted mean cycle length increase (2.38 days, 98.75% CI 1.52–3.24), and 10.6% had an increase in cycle length of 8 days or more compared with 4.3% in the unvaccinated cohort ($P<0.001$). This may imply that COVID-19 vaccination has a larger impact on menstrual regularity when both doses are administered within the same menstrual cycle. The authors highlight that the study did not provide answers to other questions about changes in menstrual cycles, such as menstrual symptoms, unscheduled bleeding, and changes in the quality and quantity of menstrual bleeding. The publication is therefore not directly relevant for this signal evaluation.

Trogstad, L. et al.: Increased Occurrence of Menstrual Disturbances in 18- to 30-Year-Old Women after COVID-19 Vaccination. 01 January 2022.

MAH's response:

A preprint of a study from the Norwegian Institute of Public Health asked a pre-existing cohort of 5,688 Norwegian women between 18 – 30 years of age whether they had experienced specific menstrual changes in the cycles before and after each vaccine dose. Over 90% of the women were vaccinated with 2 doses of Comirnaty (43.5%) or Spikevax (48.1%). The high level of variation in normal cycles is underlined by the finding that 37.8% of participants reported at least one change from normal even in pre-vaccination cycles. Of the vaccinated women who experienced menstrual disturbances, the study identified heavier than normal bleeding as the change most associated with vaccination (first dose: RR 1.9, 95% CI: 1.69 to 2.13; second dose: RR 1.84, 95% CI 1.66 to 2.03).

Changes in reported bleeding patterns before and after the first and second vaccine dose are presented in Table 1 and Table 2, respectively. The proportion who reported heavier periods than normal was higher after the first vaccine dose than before vaccination, 13.6% and 7.6%, respectively. After the second dose, the incidence of various disturbances increased.

Menstrual changes after the first dose were short-lived and returned to normal by the time for vaccination with the second dose, approximately two to three months after vaccination with the first dose. Among women who reported menstrual changes after the first dose, 92.3% were also vaccinated with Dose 2. Among women who did not report any disturbances after the first dose, 94% were vaccinated with Dose 2. Among women who experienced changes after the first dose, almost two out of three women also experienced them after the second dose. Data about the duration of menstrual changes after Dose 2 are not yet available, but this will continue to be monitored.

Table 1. Changes in Reported Bleeding Patterns Before and After Vaccination Among 3972 Menstruating Women Aged 18-30 Years, Before and After First Vaccine Dose

Menstrual Change	Before First Vaccine Dose (Unvaccinated)	After First Vaccine Dose (Vaccinated With at Least 1 Dose)
Heavier than normal	7.6%	13.6%
Longer duration than normal	9.3%	12.5%
Shorter interval between periods	9.5%	12.0%
Longer interval between periods	10.3%	10.9%
Unexpected breakthrough bleeding	13.8%	14.2%
More painful periods than normal	11.4%	14.6%
Period-like pains without bleeding	18.3%	15.8%

Source: Table 2 from Trogstad et al.[1]

Table 2. Changes in Reported Bleeding Patterns Before and After Vaccination Among 3507 Menstruating Women Aged 18-30 Years, Before and After Second Vaccine Dose

Menstrual Change	Before Second Vaccine Dose (Unvaccinated)	After Second Vaccine Dose (Vaccinated With at Least 2 Doses)
Heavier than normal	8.2%	15.3%
Longer duration than normal	8.2%	14.3%
Shorter interval between periods	7.9%	14.3%
Longer interval between periods	8.4%	10.5%
Unexpected breakthrough bleeding	10.0%	15.1%
More painful periods than normal	9.8%	16.0%
Period-like pains without bleeding	11.8%	16.5%

Source: Table 3 from Trogstad et al.[1]

The MAH states that the study has several limitations. The data are self-reported, and the MAH argues that it is conceivable that women who experienced menstrual changes after the first dose were concerned and thus more likely to report this also after the second dose, compared with women who did not experience menstrual disorders after the first dose. Between 50 and 60 of the women previously had COVID-19. These were excluded from analysis.

PRAC Rapporteur's comment

The study by Trogstad et al. included 5,688 women. The participants are part of an on-going cohort study (The Young Adult Cohort). They were randomly drawn from the National Population Registry and recruited in May 2021. Thus, recruitment is not driven by an incentive to participate caused by already experiencing menstrual disturbances, thereby minimizing the effects of selection bias. The questionnaire included several topics not related to menstruation to be answered prior to the menstrual disorders-questions excluding awareness of these disturbances as a primary incentive to respond. The study compares data before and after vaccination, where each individual is its own control. Applying this type of self-control case series design adjusts for the effect of confounding factors. The risk of recall bias is a limitation. Median interval from first vaccine dose to fill-in date was 114 days (IQR 106-133 days), while median interval from second vaccine dose to fill-in date was 63 days (IQR 56-83 days). Notably, to make sure the observation time after vaccination was long enough for the outcome to occur, only persons with intervals 42 days or longer were included. However, 57.7% of menstruating women participating in the cohort tracked their menstruation using an app and had available data in aiding their answers, they were therefore not solely dependent on recall. Moreover, some awareness bias due to media attention on reported menstrual bleeding disturbances may not be ruled out.

A significant increase in heavy menstrual bleeding was reported following COVID-19 vaccination. The estimated relative risk of more heavy menstrual bleeding than usual after the first vaccine dose was 1.9 (95% CI 1.69 - 2.13), and 1.84 (1.66 - 2.03) after the second vaccine dose. Women who had experienced more heavy bleeding than usual after the first vaccine dose had a high risk of having the same reaction after the second vaccine dose, 63.4%.

Of note, not all events related to menstrual disorders showed a change after vaccination, indicating that participants were not overall biased against menstrual cycle changes.

Supplementary data were made available during the assessment of this response (please see section 3.1.1). Trogstad et al. performed additional analysis stratified by concurrent medical conditions (diseases in uterus/cervix) and concomitant medication (contraception). These analyses did not identify any other factors than vaccination that could explain the increased risk of heavy menstrual bleeding seen in the main analysis. Analysis stratified by vaccine type showed that results for Comirnaty were consistent with the overall analysis. Heterologous vaccination (Comirnaty then Spikevax or Spikevax then Comirnaty) yielded similar results as homologous vaccination (Comirnaty or Spikevax only).

The MAH recites some details from the study, but a proper discussion is lacking. The statement that "it is conceivable that women who experienced menstrual changes after the first dose were concerned and thus more likely to report this also after the second dose" is not endorsed as an argument to discard the findings, as a significant increase was already noted following the first dose. Vaccination with dose 2 was not affected by experience of heavy menstrual bleeding following dose 1. Further, questions of menstrual disturbances following both dose 1 and 2 were answered one time in the same survey. Thus, the MAH's arguments regarding nervosity in participants are not relevant.

In conclusion, the design of the study has sought to mitigate main limitations and enables valid support for an association between COVID (mRNA) vaccination and various menstrual cycle changes, including heavier than normal menstrual bleeding.

Netherlands Pharmacovigilance Centre (Lareb):

MAH's response:

A publication by the Netherlands Pharmacovigilance Centre Lareb described the number of cases of heavy menstrual bleeding, and the rate per 100,000 vaccinations, by age group, vaccine platform and number of doses, providing an overview of all reports of menstrual disorders following COVID-19 vaccinations. Heavy menstrual bleeding was the second most common reported category of menstrual abnormalities (after amenorrhea/oligomenorrhea).

Age group	10-14	15-19	20-45	45+	Unknown	Total
Reporting rates per 100 000 (dose 1, dose 2)	21.0, 9.9	23.9, 20.3	90.1, 87.5	8.5, 13.2		36.8, 37.0
Number of reports (total, dose 1, dose 2)	49, 35, 14	137, 80, 57	2.742, 1.475, 1.267	600, 240, 360	5, 3, 2.	3.533

It should be noted that the data should not be interpreted as incidence rates. The MAH has not provided their own discussion and conclusion on this publication, but has referred statements from the authors.

PRAC Rapporteur's comment

The data are from the spontaneous reporting system in the Netherlands. There is no backlog in the Dutch system, hence these numbers represent what has been reported. The Netherlands is at the moment the country with the second most submitted reports worldwide.

Data provide an overview over cases and the extent of these events, which is also discussed in Q4. However, this is not a study per se as no research questions are asked or analysed.

Medicine and Healthcare Products Regulatory Agency. Coronavirus vaccine—weekly summary of Yellow Card reporting. 13 Jan 2022.

MAH's response:

The MAH referred to this article which states that more than 36,000 reports of menstrual changes or unexpected vaginal bleeding following COVID-19 vaccination have so far been made to the yellow card surveillance scheme run by the UK Medicine and Healthcare Products Regulatory Agency (MHRA). But as cycles vary naturally and the MHRA does not collect comparison data from unvaccinated people, these data cannot be used to establish whether menstrual changes increase after vaccination. Currently the MHRA concludes that current evidence does not support a link between changes to menstrual periods and COVID-19 vaccination in the UK, and it continues to advise that anyone noticing a change to their periods that persists over several of cycles, or who has any new vaginal bleeding after the menopause, is treated according to the standard clinical practice.

PRAC Rapporteur's comment

This information is updated regularly. As of May 5th the total of ICSRs submitted is 39,746 relating to a variety of menstrual disorders after all three of the COVID-19 vaccines.

The publication does not provide novel information that enables further assessment of this issue.

Male V. Effect of COVID-19 vaccination on menstrual periods in a retrospectively recruited cohort.

MAH's response:

The MAH refers briefly from a preprint article of a study on a retrospectively recruited cohort of 1,273 participants over the age of 18 using a web-based form to collect details of their menstrual cycle, gynaecological medical history, and vaccination dates. The MAH states that the authors concluded that they were unable to find evidence supporting a causal association between COVID-19 vaccination and menstrual changes. In particular, the authors examined a subset of participants who were not using hormonal contraception and found no association between the timing of vaccination and flow of the next period. Additionally, there was no association between the brand of vaccine and any self-reported changes to timing or flow of the next period. The MAH writes that limitations included a study population primarily from the UK and the nature of the retrospective recruitment that might motivate more participation by women who had noticed changes in their periods.

PRAC Rapporteur's comment

The PRAC Rapporteur does not entirely agree with the MAHs interpretation of the study authors' conclusion. The authors write "In this dataset, we were unable to detect strong signals to support the idea that COVID-19 vaccination is linked to menstrual changes". The study is inconclusive, and should not be used to either to dismiss or support a possible causal association because of the retrospective questionnaire-based design without a control group, and the research questions. This is also stated by the authors, who writes that prospectively recruited studies may be able to find associations that they were not powered to detect.

Only patients who had a record of their normal menstrual cycle were included, and women were asked questions whether menstruation had changed following COVID-19 vaccination. It is a limitation that data were not gathered for cycles before and after vaccination separately, but only as change reported by the participants. Analysis thus included only comparison between subgroups (vaccine type, concomitant contraception or medical conditions, timing of vaccination and dose 1 vs dose 2), not the extent of change following vaccination per se. Menstrual flow was reported to be increased in 32% of women who received vaccination with Comirnaty. Due to the lack of control group, this finding was not further analysed or discussed by the authors.

Nguyen BT, Pang RD, Nelson AL, et al. Detecting variations in ovulation and menstruation during the COVID-19 pandemic, using real-world mobile app data.

MAH's response:

The MAH briefly mentions Nguyen et al, who aimed to study whether the pandemic had an effect on women's menstrual cycles. 214 426 cycles were analysed from 18 076 app users. March-September 2019 were compared to March- September 2020.The authors concluded that the COVID-19 pandemic did not induce population level-changes to ovulation and menstruation among women. The MAH did not provide a discussion of these results.

PRAC Rapporteur's comment

The pandemic stress has been proposed by some, including the MAH in their response, as a partial explanation for the observed changes in women's cycles. The study by Nguyen et al indicate that the pandemic in itself did not cause disturbances in women's menstrual cycles. The pandemic stress should therefore not be included as a confounding factor when interpreting data from other studies addressing menstrual disorders following COVID-19 disease and/or vaccination.

Alvergne A, Kountourides G, Argentieri MA, et al. COVID-19 vaccination and menstrual cycle changes: A United Kingdom (UK) retrospective case-control study.

MAH's response:

The publication by Alvergne et al (preprint available in November 2021) concludes that following vaccination for COVID-19, menstrual disturbance occurred in 20% of individuals in a UK sample of 4,989 individuals. The MAH did not provide a discussion on the findings of the study, but emphasizes that out of 33 variables investigated, smoking and a previous history of SARS-CoV-2 infection were

found to be risk factors while using oestradiol-containing contraceptives was found to be a protective factor. Further, the MAH refers to the authors stating that most menstruating women did not experience a change in their menstruating pattern and the MAH describes this as reassuring.

PRAC Rapporteur's comment

The study by Alvergne et al. is a secondary analysis of a retrospective online survey. 26,710 women aged 18-43 participated in the study, and 4,989 vaccinated individuals were selected for analysis (47% received Comirnaty). The study was initially designed to evaluate the impact of COVID-19 pandemic but was amended to include effects of COVID-19 vaccination. Main outcome measure was report of any menstrual change (yes/no), with an added qualitative description of the reported changes.

To limit selection bias, the title of the survey was general: "Female reproductive health and the COVID pandemic". The study was conducted in March 2021, which with respect to selection bias, could be considered an advantage as there was little media attention at that time.

Following vaccination, menstrual disturbances occurred in overall 20%: 6.1% of individuals reported more disruption, 1.5% reported less disruption and 11.5% reported "Other changes". The MAH's discussion focuses on other known factors linked to menstrual disturbances, e.g. smoking and contraceptive use. As the study had a self-control design, contribution of other factors is adjusted, and the discussion should rather have focused on the main finding. The MAH's interpretation that corresponding result (80% did not have a menstrual disturbance) is reassuring, is not endorsed and appears as a misinterpretation of the result.

It is acknowledged that the study has certain limitations. The lack of a control group limits conclusions on causality. Additionally, the results are presented for all types of menstrual change. Based on the qualitative descriptions provided by the participants, an analysis of the most common words used (e.g. heavy bleed), is presented, but results must be interpreted with caution.

To conclude, the study provides little information that allow for any strong interpretation in any direction.

PRAC Rapporteur's overall assessment of available literature

The MAH detected 7 publications for review. Their search criteria were not presented, and it is therefore not possible to evaluate whether all relevant publications were captured. The Assessors therefore performed a systematic search that did not detect further relevant publications. Overall, the amount of publications and research in this topic is scarce.

Regarding the presentation of evidence: The MAH did not present a detailed structured review of the published studies with a separate evaluation and conclusion on each study which would have been expected.

Main challenges for epidemiological research are recall bias and, depending on study design, selection/participation bias. This must be taken into account when evaluating the results. However, as a result of mass vaccination, a proper unvaccinated control group is challenging to obtain.

Regarding selection bias, participants in the studies by Alvergne, Lee and Male were recruited after the vaccination took place and after media attention rose. It cannot be excluded that experiencing

menstrual disorders formed an incentive to participate. This does not imply that the reported results are not valid but may have led to an overestimation of actual incidences.

The prospective study by Edelman et al. investigated cycle and menses lengths, showing a small (< 1 day) but significant increase in cycle length when comparing cycles before/after COVID-19 vaccination. The study was not designed to evaluate the quantity of menstrual bleeding and is therefore less relevant for the current signal evaluation.

The studies by Lee et al., Alvergne et al. and Male were all questionnaire-based and retrospective, and were not designed to detect a causal association due to the lack of control groups. Their study design and the research questions asked limits the relevance for the overall assessment.

Contrary to, this, the Trogstad-study was based on an existing cohort with participants already recruited (age 18-30). Therefore, the selection bias is minimized. The survey was distributed after most of the participants had been vaccinated with two doses. Response rate was 68.4% (n = 5,688) and the questionnaire was designed to exclude experiencing menstrual disturbances as a motivator to complete the form. The study applied a self-control case series design analysis, where the possible contribution of other confounding factors is corrected since each participant functions as their own control. Further, the study also corrected for COVID-19 disease: A low number of women had a history of COVID-19 infection and excluding these from analysis did not change risk estimates.

Considering the above, Trogstad et al. is considered the most relevant study that is currently available to assess a possible association between heavy menstrual bleeding and COVID-19 vaccination. Reported heavy menstrual bleeding was significantly increased following vaccination (first dose: RR 1.9, 95% CI: 1.69 to 2.13; second dose: RR 1.84, 95% CI 1.66 to 2.03).

Additional analysis from this study have been submitted to the PRAC Rapporteur during the assessment phase. The analyses did not identify any factors that could explain the increased risk of heavy menstrual bleeding seen in the main analysis.

Data from another study (not yet published), by Caspersen et al. in 12-15-year-old Norwegian adolescents were made available during the assessment phase and have been included in this report. This study showed a significantly increased occurrence of heavier bleeding when comparing the most recent menstruation prior to vaccination with the first menstruation after vaccination (relative risk: 1.61, 95% CI: 1.43 to 1.81). While menstruation disorders were overall common also in the unvaccinated group (22.3%), an increase was noted in vaccinated group in the first cycle after vaccine (from 22.6% to 25.1%). The results are consistent with the findings in the study by Trogstad et al and the consistency in the studies (across age groups) provides support for a possible association between heavy menstrual bleeding and COVID-19 vaccination.

Overall, few studies have been performed to address this issue and literature is limited. The PRAC assessors consider that the review of the literature that is available supports at least a possible relationship between heavy menstrual bleeding and vaccination with Comirnaty.

Question 3: Case overview

A case overview was included in the response to Question 4

Question 4: Case review

MAHs response:

Pfizer's safety database contains cases of adverse events reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of serious adverse events reported from clinical studies regardless of causality. The Pfizer safety database was searched for all BNT162b2 vaccine cases received through 15 February 2022 using the MedDRA version 24.1 search criteria: PT: Heavy menstrual bleeding.

A total of 23,659 cases were identified from the database using the search criteria. Most of the cases (99.7%) were spontaneous reports, 47 (0.2%) were clinical study reports and 29 (0.1%) were solicited reports. Most of the cases, 16,940 (71.6%), were non-serious cases and the remaining 6719 (28.4%) were serious cases. Most of the cases (91.2%) were nonmedically confirmed and the remaining 2073 (8.8%) were medically confirmed.

The case distribution by age is shown below:

	Age Range	Number of Cases	Percentage (%)
Min = 6 Years	Less than or equal to 17 years	519	2.2
Max = 84 Years	18-30 years	6815	28.8
	31-50 years	13197	55.8
Mean= 34.7	51-64 years	926	3.9
	65-74 years	6	0.0
	Greater than or equal to 75 years	4	0.0
n=21454	Unknown	2192	9.3

The top ten reporting countries is shown below:

Country Where Event Occurred Top 10 Case Count	Number of Cases	Percentage (%)
UNITED KINGDOM	8429	35.6
NETHERLANDS	4610	19.5
GERMANY	3669	15.5
NORWAY	1172	5.0
FRANCE	1057	4.5
UNITED STATES	710	3.0
DENMARK	549	2.3
SPAIN	526	2.2
AUSTRALIA	458	1.9
CANADA	367	1.6

When reported, the clinical outcome of the PT 'Heavy menstrual bleeding' was reported as not resolved at the time of reporting in 9,995 cases, resolved/resolving/resolved with sequelae in 8,574 cases and unknown in 5,433 cases.

Out of the 23,659 cases, 523 were medically confirmed, serious cases. Within these medically confirmed, serious cases, there were 126 cases in patients younger than 17 years old and older than

45 years old which were excluded from further detailed review because anovulatory bleeding is a potential cause of acute menorrhagia in the adolescent and perimenopausal patient.

Within the 397 remaining cases, 186 of them did not include medical history and/or information on risk factors; therefore, these were removed from the list of cases for further evaluation.....

Within the 211 remaining cases:

- there were 46 that reported use of hormonal contraception or an intrauterine device.
- an intrauterine device was involved in 9 cases and 4 of these cases provided details of the type of intrauterine device as copper.
- heterologous primary or booster vaccination schemes were noted in only 2 cases.
- only 4 cases reported information on when vaccination took place relating to the time of ovulation. In 1 case the patient was vaccinated during the luteal phase and in 3 the patients were vaccinated during the follicular/proliferative phase. No pattern related to cycle was seen in this small number of reports

The 211 medically confirmed serious cases providing medical history was further analyzed to identify cases with a medical history of confounders such as blood coagulopathies, malignancies, hypothalamic or pituitary disorders, endocrine gland disorders, endometrial dysfunction, and/or confounding concomitant medications such as gonadal steroids, anticoagulants, aromatase inhibitors, selective estrogen/progesterone receptor modulators, medications associated with hyperprolactinemia, that may represent an alternative etiology for heavy menstrual bleeding. Within the case list, 71 cases were considered for further evaluation as these were not confounded by reported medical history and/or concomitant medications.

PRAC Rapporteur's comment

A large number of ICSRs has been excluded from the analysis and subsequent causality assessment due to confounding information regarding concomitant medications or medical history. The presence of potential confounding factors in a real-world population is not unexpected, but as many factors in theory could affect menstrual cycle, there is a risk of excluding cases from further review with clinically relevant case details or temporal relationship that might have relevance for the assessment.

186 of 397 cases were excluded from review because they did not include medical history and/or information on risk factors. Similarly, excluding cases without explicit information on the lack of specific risk factors runs a risk of missing case reports that could be relevant to include in the causality assessment.

Six cases were also excluded because of concomitantly reported adverse events such as Guillain-Barre-syndrome, immune thrombocytopenia, hypersensitivity, nosebleed, endometriosis), and 2 were excluded because they were breast feeding. It is not entirely clear why concomitant Guillain-Barre syndrome or hypersensitivity would warrant exclusion from further analysis, as to the PRAC Rapporteurs knowledge, these conditions are not strongly linked to menstrual disturbances. With regards to nosebleed, this could potentially be seen as a co-manifestation of the same mechanism causing heavy menstrual bleeding, thus it should not be routinely dismissed.

Of the remaining 65 cases, 48 more cases were excluded from review because they reported insufficient information on previous menstrual patterns.

PRAC Rapporteur's comment The MAH has excluded 48 cases because they lack data on previous menstrual pattern. This approach is not supported.

The 16 remaining cases are described in detail, including a WHO-UMC Causality assessment and a justification of causality category. Cases were classified as follows:

- Six unassessable
- Four unclassifiable
- Four possible
- Two unlikely

PRAC Rapporteur's comment

The MAH's interpretation of the criteria for classifying ICSRs according to the WHO-UMC causality assessment system is not supported. The PRAC Rapporteur considers that the criteria have not been correctly interpreted, and accordingly the ICSRs have been systematically classified at a lower level than what would be expected.

The MAH has classified cases as "unlikely", despite plausible temporal relationship, due to the presence of alternative causes, such as concomitant medications or disease. In the WHO-UMC causality assessment system, the category "unlikely" is described as "*A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations*.", whereas the category "possible" is described as: "*A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear*"

As an example, one case has been classified as "unlikely". The rationale given by the MAH states that "there is a reasonable relationship to vaccination, however, alternate causality may be hypersensitivity and/or resumption of period post IU device removal". Although it is agreed that other causes could not be ruled out in this particular case, this is not sufficient to classify a report as unlikely. In this case a plausible temporal relationship to vaccination exists, thus the category "unlikely" does not appear to be the appropriate category despite other possible explanations present in the case description.

The MAH has also classified other cases as unassesable due to lack of information on details "such as migraine prophylaxis and skin infection/cellulitis treatment". According to the case description the irregular menstruation appeared on the day of the vaccination, whereas unspecified migraine prophylaxis was started 3 months post vaccination. It is rather unclear why a treatment with no temporal relationship would render this case report as unassesable.

In general, the MAH has classified cases as unclassified or unassessable due to lack of lab test and clinical course details. By demanding this level of detail to assess causality, the MAH sets the bar for ICSRs unreasonably high, thereby rendering a large proportion of the ICSRs unassessable or unclassifiable. The PRAC Rapporteur does not agree with this approach.

Overall, due to the MAHs approach as detailed above, the MAHs causality assessment adds little value to the assessment of the signal.

MAHs overall summary of the case review:

Overall, 23,659 cases of heavy menstrual bleeding were reported to the Pfizer safety database in the context of over two billion of Pfizer/BioNTech COVID-19 vaccines doses distributed. Of the 17 cases individually assessed, 6 were unassessable, 4 were unclassified, 4 were possible and 2 were unlikely causally related using the WHO-UMC causality assessment system.

PRAC Rapporteur's comment

The review should have prioritised serious **and/or** medically confirmed cases as specified in the LoQ, however the MAH has selected medically confirmed **and** serious cases. From a search result of 23,659 cases, the MAH has selected 523 cases for review (those that were medically confirmed) and has provided details of 16 cases (Not 17 as was stated by the MAH in their summary). Hence, an unknown number of serious cases that are not medically confirmed have been left out of the review.

There might be a substantial number of reports lacking. A search in Vigibase as of 19 April 2022 yielded 4,508 **serious** reports of PT 'Heavy Menstrual bleeding' reported from consumer/non health professionals for the product Comirnaty globally. Several thousands of reports have therefore been left out of the review.

Regarding the MAH's main conclusion: It is agreed that the exposure is indeed vast. However, taking into account the backlog in the processing of ICSRs (not stated by the MAH), and underreporting, the numerical comparison of 23,659 cases with 2 billion doses is not correct.

In Eudravigilance there are currently 186 reports coded with positive rechallenge (as per 29.04.2022).

Overall, due to the strict criteria for excluding cases, and the method used in assessing causality, the PRAC Rapporteur considers the MAH's case review of limited value in the assessment of the signal. However, as it is uncertain if any further in-depth analysis of ICSRs would provide further evidence at this stage of the assessment, no further case review is requested.

Observed vs Expected Analysis

Expected heavy menstrual bleeding cases for the O/E analyses were derived using background incidence rates from a study in the Netherlands that included females who consulted their general practitioner for heavy menstrual bleeding during 2004-2013. This study reported a mean annual incidence rate of 9.3 per 1000 person years (95% CI 8.5-10.2) for females aged 10-59 years. Based on the age-specific background incidence rates provided in that study, all O/E ratios across all stratifications were below 1, suggesting that the number of reported cases is not higher than expected compared to unvaccinated persons.

Table 6. Observed to Expected (O/E) Analysis for Heavy Menstrual Bleeding Reported through 15 February 2022 in the US and EEA

Event	Observed Cases	Time at Risk (PY)	Background Rate Per 100,000 PY[a]	Expected Cases	O/E Ratio	95% CI
21-day risk window						
Females 15-34 years	9314	7,049,936	735	51,817	0.180	0.176, 0.183
Females 35-45 years	6467	4,309,700	1300	56,026	0.115	0.113, 0.118
All females 15-45 years	15781	11,359,636	923	104,849	0.151	0.148, 0.153
42-day risk window						
Females 15-34 years	11047	10,753,962	735	79,042	0.140	0.137, 0.142
Females 35-45 years	7724	6,618,653	1300	86,043	0.090	0.088, 0.092
All females 15-45 years	18771	17,372,615	923	160,350	0.117	0.115, 0.119

a. Background rate source: van den Brink MJ, Saaltink AL, Groenhof F, Kollen BJ, Berger MY, Lisman-van Leeuwen Y, Dekker JH. Incidence and treatment of heavy menstrual bleeding in general practice. Fam Pract. 2017 Nov 16;34(6):673-678. doi: 10.1093/fampra/cmx050. PMID: 28586411. Age specific incidence rates are provided in Table 2 of the publication; we used the average of rates for ages 15-24 and 25-34 for the 15-34 age group, the 35-44 rate for the 35-45 age group, and the average of the incidence rates for 15-24, 25-34, and 35-44 for the overall 15-45 age group.

PRAC Rapporteur's comment

The MAH has not adjusted for underreporting or the backlog. This issue is further exacerbated by the fact that the study used to calculate the incidence background rate relies on a different age group, from a different geographic population than the dataset used to compile observed cases, which could all bias the estimates both through the actual occurrence of heavy menstrual bleeding and through underreporting behaviour linked to the spontaneous surveillance systems. Such potential bias should have been addressed through additional uncertainty analyses, for instance using a stratification by country or region. Here, the considerably low O/E ratio reported do not appear realistic, as it suggests the occurrence of heavy menstrual bleeding being drastically lowered after the second injection of Pfizer/BioNTech COVID-19 vaccine, i.e., almost divided by a factor of 5 to 10 compared to the background rate. Hence, it is difficult to draw any robust conclusions based on the current analyses. Additionally, the MAH has not provided details on how the time at risk (PY) has been calculated. Due to these limitations, in particular the uncertainty regarding the backlog, the applicability of the O/E-analysis is uncertain.

Question 5 – Mechanism of Action

Abnormal uterine bleeding (AUB), including heavy menstrual bleeding, have widely varying prevalence rates (3%-30%) in the medical literature. This is thought not to be because the events are rare, but because they are not always reported by women to their HCPs. Broadly, classification of AUB can be thought of as structural or non-structural and clinical assessment including imaging, lab and histopathological data can lead to many subclassifications. Menstruation is described as an inflammatory process and the change in endometrial function during the cycle is associated with changes in endometrial and systemic inflammatory cells and cytokines. The inflammatory process is initiated by hormonal changes that direct immune cells to the endometrium to secrete inflammatory and other mediators. It is thought that these mediators contribute to events like endometrial breakdown, vasodilation, bleeding, changes in vascular regeneration and anticoagulation, and subsequently, the signs and symptoms of AUB. How immune cell composition changes during the entire menstrual cycle, in disease states and non-disease states, is not well understood at present. ¨'

PRAC Rapporteur's comment

The MAH has provided a general discussion on a potential mechanism of action, which is supported.

Question 6 – Exposure in Females of Childbearing Potential

The MAH estimates that there was a total of 84,994,706 females aged 15-45 years who received at least one dose of Comirnaty in the US or EEA countries through February 15, 2022. This estimate is based on data from the CDC in the US and ECDC in the EEA.

PRAC Rapporteur's comment

The exposure of females in US and EEA is estimated at 85 million doses.

MAH's summary and conclusion

The MAH concludes that overall, the data do not support that heavy menstrual bleeding is caused by BNT 162b2 vaccine at this time. Therefore, no changes to the product information and/or the risk management plan are warranted at this time. The topic will continue to be monitored using routine pharmacovigilance.

The MAH has included the following key points:

- The number of reports in the clinical trials were relatively small when considering the size and the length of the study.
- The medical literature reveals that menstrual abnormalities are very common, as well as the pandemic stress, anxiety and depression.
- A clear pathophysiological pathway is not understood.
- The study by Edelman et al. that did not support a significant effect of vaccination on the number of days of menstrual bleeding.
- 4 of the >23,000 cases of heavy menstrual bleeding were assessed as possible.
- The O/E ratios do not indicate that reported events are higher than expected based on background incidence rates.

PRAC Rapporteur's overall comment

Clinical trials

It is agreed that the number of reports from the clinical trial is low. However, it could be questioned whether the trial was designed to detect this safety issue. The reporting was unsolicited. The reaction is frequently occurring in the general population. It is therefore plausible that female participants experiencing changes in their menstrual pattern or menstrual bleeding after vaccination would not have intuitively suspected it related to the vaccine – bearing in mind that this reaction is not commonly associated with vaccination.

Secondly, the age of the trial participants is highly relevant information, and the MAH has not provided this information even though this was specifically requested. The number of women in the trial is not sufficient information –the number of women of childbearing age is relevant for this signal.

The MAH has disregarded that there was a numerical imbalance in the clinical trial; in the placebo-controlled trial it was 4 (vaccine) vs 2 (placebo) cases. In a trial of this size, risk factors are assumed to be evenly distributed. Therefore, a numerical imbalance should not be ignored.

To summarize, data from the clinical trial are not sufficient to allow for a proper assessment of a possible causal association as the MAH has not responded to the issue correctly.

Overall, information from clinical trials does not provide data that is supportive in neither establishing a causal association nor dismissing one.

Published literature

The MAH states that the published literature reveals that menstrual abnormalities are common, which is endorsed. The MAH mentions the pandemic stress as an explaining factor behind reported menstrual disturbances, even though data provided by the MAH (Nguyen) indicate that the pandemic did not have any influence on the menstrual cycle.

In the MAH's summary and conclusion, the study by Edelman et al. is listed specifically, which investigated cycle/menses length, and not flow/volume. This study is therefore not considered by the assessors as the most relevant study for 'heavy menstrual bleeding' which is being evaluated.

Overall, available literature on this topic is scarce. Most studies have not been optimally designed to investigate heavy menstrual bleeding following COVID-19 vaccination and methodological limitations constrain firm conclusions.

In this aspect, the study by Trogstad et al. appears as the most robust. Even though it is not free of methodological weaknesses, it has sought to adjust for selection bias by using an already existing cohort and for confounding factors of constant nature by applying an SCCS analysis.

The study also shows that COVID 19 vaccines are associated with increased menstrual bleeding. Subsequent analysis did not identify any factors, including diseases in cervix/uterus, positive SARS-COV-2 or use of contraceptives, that could explain the increased risk of heavy menstrual bleeding seen in the overall analysis.

A similar finding of heavy menstrual bleeding following one dose of Comirnaty was shown in a 12-15 year cohort, which show consistency between age groups and cohorts (Caspersen et al., supplementary information made available during the assessment).

Pathophysiologic pathway

The MAH states that a pathophysiological pathway is not yet understood, which is endorsed. However, the pathophysiological mechanisms of myocarditis and pericarditis which are listed reactions in the SmPC, are not understood either. The limited knowledge regarding the pathophysiological pathway is considered to neither strengthen nor weaken the signal.

The Case Review

The MAH emphasizes that only 4 ICSRs were assessed as possibly related to the vaccine, from >23,000 ICSRs. The MAH's review of the >23,000 ICSRs is discussed in detail in the relevant section. The assessors disagree with the selection of cases and the evaluation. The MAH has eliminated the majority of the ICSRs from review: in total 99.94% of reports have been dismissed. The methodology of the MAH's review is not supported. The causality assessments are not endorsed, this is thoroughly justified in the relevant section. Due to the method used by the MAH, the case review has limited value in the assessment of the signal. It is acknowledged that spontaneous reports have severe limitations in assessment of causality, however, the large number of reports, many cases with positive rechallenge, and single cases with strong temporal relationship could indicate a potential causal relationship or at least a reasonable possibility.

The O/E-analysis

The MAH has submitted an observed to expected analysis with O/E-ratios below 1. However, due to the lack of information regarding the MAH's calculation of time at risk, and the uncertainty related to the backlog of ICSRs, the applicability of this analysis is difficult to ascertain. Additionally, the study chosen to calculate background incidence could bias the estimates and has not been addressed through uncertainty analysis. The considerably low O/E-ratios does not appear realistic, and it is difficult to draw any robust conclusions based on the current analysis.

Summary and conclusion

Overall, data from the clinical trials identified a numerical imbalance, and thus cannot be used to rule out a causal relationship. Data from spontaneous reports, and in particular information from literature, and the additional data provided by Caspersen et al and Trogstad et.al. indicate a potential causal relationship between vaccination with Comirnaty and heavy menstrual bleeding. Having considered the totality of available data, the PRAC Rapporteur considers that a causal relationship is a reasonable possibility.

The scope of a signal assessment procedure is not to necessarily conclude with absolute certainty on a causal association. The SmPC guidance document states that the SmPC section 4.8 should include information when there is at least a reasonable possibility of a causal association. The PRAC Rapporteur concludes that current available evidence supports a possible causal association and that this criterion is fulfilled, and the SmPC and PIL should be updated to reflect current knowledge.

3.2. Rapporteur's proposed recommendation

Based on currently available evidence the PRAC Rapporteur considers that the SmPC/PIL should be updated with information regarding heavy menstrual bleeding. The MAH is asked to propose a frequency category.

The PRAC Rapporteur considers that "heavy menstrual bleeding" should be listed in section 4.8 of the SmPC

Text for SmPC

Section 4.8: Heavy period.

Text for PIL

Section 4 (possible side effects): heavy period

3.3. Comments from other PRAC members and MAH(s)

Comment from Member State (MS11)

Based on the currently provided information we do not agree with the PRAC Rapporteur NO's proposal to add 'Heavy period' to the SmPC section 4.8. The current assessment report does not include sufficient supporting information to underpin this recommendation.

Considering the high background rate of the events irrespective of vaccination a coincidental finding based on temporal association cannot be excluded based on the currently available evidence.

Clinical trial evidence

In isolation [without considering confounding, risk factors, biological plausibility, consistency of available evidence etc], a numerical imbalance is not sufficient to establish causality.

The MAH should provide a more detailed discussion regarding the numerical imbalance of the clinical trials – 9 (vaccine) vs 3 (placebo), and the imbalance 4 (vaccine) vs 2 (placebo) in the placebo-controlled portion of the C4591001 study. This discussion should at least include (but not limited to): case details *i.e.* number of females of childbearing potential, baseline characteristics, risk factors, age, medical history and investigator's and/or MAH's evaluation of causality.

Literature

In line with the CMS comments from MS12, MS10, MS1 and our assessment of literature the currently available scientific literature is considered inconclusive and has too many limitations to support an (at least reasonably possible) causal relation.

Case review

Lack of detailed information (*i.e.* total number of supportive *and* unsupportive cases, case IDs, narratives, WHO causality scaling etc) precludes full appraisal of the strength and totality of evidence.As a minimum, in-depth assessment of the 71 cases that were considered by the MAH for

further evaluation [*i.e.* the cases not confounded by reported medical history and/or concomitant medications] should be included in the assessment report.

Regarding the 186 rechallenge cases, it should be clearly stated how many of these were informative, supportive, unsupportive, and uninformative/unassessable for causality.

If the Rapporteur considers the MAH's triage and review of relevant cases insufficient, additional data or more critical evaluation should be requested from the MAH, or - if preferred by the Rapporteur -, Rapporteur's own critical appraisal of cases can be included in the assessment report. To understand the Rapporteur's conclusion, it would be helpful to see the cases where the Rapporteur disagrees with the MAH regarding WHO causality scaling as well as the number of supportive [*i.e.* WHO probable/possible] *and* unsupportive [WHO unlikely/unassessable] cases.

PRAC Rapporteur's comment

Clinical trials data: The comment from the MS that seen in isolation the numbers from the clinical trials are not sufficient to establish causality, is agreed upon as has been discussed in the assessment report.

Literature: We agree that there is limited available data from the literature, and that the available studies have limitations. However, we are of the opinion that the review of available literature, including the unpublished data presented in the AR, provide support for at least a reasonable possible causal association.

Case review: The MS states that 71 cases should be included in the AR as a minimum. However, the MAH did not submit details of the 71 cases that were considered by the MAH for further evaluation, hence they were unavailable, and therefore not included in the assessment report. The MAH submitted details of 16 cases. Regarding the 186 rechallenge cases, these were not part of the submitted data package from the MAH, but was detected in EV by the PRAC Rapporteur. Since they were not part of the response document, they have not been evaluated, but information on the number of rechallenge cases are of value, hence the PRAC Rapporteur identified this number.

The 16 cases that were described by the MAH (with disagreements as regards WHO causality assessment) were not included with full details in the AR, but were available in the response document and therefore was available to the MS.

The comment from MS11 could be interpreted as a request for an RSI, since many issues are proposed clarified. We are of the opinion that these issues (more details on rechallenge cases, a more critical review of relevant cases) would not provide essential information at this stage. We are of the opinion that the currently available data is sufficient to establish a at least reasonable possible causal association in accordance with the SmPC guideline. Therefore we do not consider that an RSI is necessary.

Comment from Member State (MS1)

The proposed recommendation by the signal lead Member State to update the SmPC section 4.8 is not endorsed. Based on the data presented in the AR, the proposal to update the PI is based on a small imbalance in clinical trials, the study by Trogstad et al. including additional confidential analyses provided by NO, and the high number of reported cases of Heavy Menstrual Bleeding. Regarding clinical trial data, the signal lead Member State concludes that the response by the MAH is unstructured and has not provided all the requested information, including age of study participants which is highly relevant, also when considering the imbalance. However, the signal lead Member State

concludes that "Overall, information from clinical trials does not provide data that is supportive in neither establishing a causal association nor dismissing one" which is endorsed.

Regarding literature, the MS1 Medicines Agency does not consider the study by Trogstad et al. (including additional confidential analyses and the provided manuscript by Caspersen et al.) to have sufficient power to support an update of the product information with heavy menstrual bleeding. MS1 Medicines Agency agrees with the study limitations already outlined by MS12, and wishes to add the following observations:

- Recall bias: It is argued by the signal lead Member State that 57.7 % of the participating women in the study used an app to track their period, and that these women were not solely dependent on recall, thereby limiting recall bias. However, the usefulness of these apps should be considered with regards to Heavy Menstrual Bleeding. The tracking and registration would be highly dependent on the interface of the app, often with few categories to indicate the daily amount of bleeding. It is considered that the main purpose of many of these apps is prediction of cycle length, bleeding period and perhaps prediction of fertile window. It should also be noted that tracking may be subjective and can be performed retrospectively.

- Information on cycle pattern: In the SCCS analysis, the last cycle before vaccination is compared to the first cycle after vaccination. It would have been useful if more information om menstrual cycle pattern had been considered. Either as an inclusion criterion (e.g. regular and normal cycle length for x cycles) or a possible stratification. Especially considering that the background incidence of variations in menstrual cycles in the study is high (37.8%).

Furthermore, the signal lead Member State included the unpublished manuscript of a study by Caspersen et al. regarding menstrual changes in 12-15-year-old adolescents after COVID-19 vaccination. This is appreciated. However, to fully take this data into consideration, it would be useful to have the complete data available. The tables and supplementary tables mentioned in the manuscript in annex II were not provided. Based on the manuscript, this study seems similar in study design to Trogstad et al., and is therefore subject to some of the same limitations. The two studies do show consistency across age groups. However, in terms of causality, the MS1 Medicines Agency considers that further studies are needed to confirm the findings in these studies.

PRAC Rapporteur's comment

The MS comments on the study by Trogstad et al, the use of apps for recalling menstrual abnormalities, and states that this is highly dependent on the interface of the app and that it has few categories. The MS states that it is considered that the main purpose of many of these apps is prediction of cycle length, bleeding period and perhaps prediction of fertile window. We agree that it would be helpful to have an overview over the most used apps, and how the interface describes menses volume, but currently this information is not available. It is also agreed that tracking is subjective and can be performed retrospectively. Please note that some apps have a push alert to remind the user to register her menstruation. Further, the MS comments on the usefulness of more information on previous cycles, for instance including only those with a normal cycle pattern, or a stratification. The women were asked if the vaccination induced a certain change (yes/no) for several types of events. A subjective noticed change in a woman's cycle could indicate that the cycle is usually predictive (if something is noticed to be changed, some form of subjective interpretation of a baseline is necessary) hence it could be argued that this is a form of selection that the MS comments.

With regards to the tables and supplementary tables to the manuscript by Caspersen et.al., they have been attached to the manuscript in annex II.

We agree that further studies to confirm the findings would have been ideal, however at this stage of the pandemic where most of the population has already been vaccinated, we consider that this is not feasible.

Comment from Member State (MS10)

The NO team is thanked for a thorough and comprehensive assessment.

It is challenging to evaluate a potential causal relationship between a vaccine and heavy menstrual bleeding, a condition that is very common and can be induced by different circumstances/events such as e.g., stress, caloric restriction, or heavy exercise. Furthermore, heavy menstrual bleeding is a subjective, not easily standardized condition. Thus, data from self-reporting or even questionnaire data are very difficult to interpret, especially, as in this case, there has been a lot of attention in the media. The aspect of heterogenous aetiology is also reflected in the publication by Lee et al, which is included in this signal evaluation, suggesting that increased/breakthrough bleeding was significantly associated with age, other systemic vaccine side effects (fever, fatigue), history of pregnancy or giving birth, and ethnicity.

The Rapporteur proposes to include "heavy period" in the SmPC section 4.8 based on one questionnaire report from the Norwegian Institute of Public Health. The study has not been peer-reviewed and is only available as a pre-print version. In this study, there was a generally high incidence of the various menstrual disturbances among menstruating women aged 18–30 years; 37.8% reported at least one change during their last period before vaccination, 39.4% reported at least one change after Dose 1, and 40.9% after Dose 2. A significantly increased risk specifically after the first dose is reported (RR1.90, CI 1.69-2.13). The authors of the study themselves conclude that the interpretation of the study results is limited by several putative confounders such as media attention, a view that can be endorsed.

The additional evidence presented in this AR, does not include data from clinical trials or cases from the MAH global database that at this stage support an at least possible causal association.

Therefore, the available data is not considered sufficient to conclude upon a reasonable causal relationship. Nevertheless, the topic should be closely monitored in upcoming PSURs.

PRAC Rapporteur's comment

The general comment from MS10 on the assessment is highly appreciated. The challenges on the evaluation of the condition "heavy menstrual bleeding" are agreed upon.

The MS comments that the Rapporteur proposes to include "heavy period" in the SmPC section 4.8 bases on one questionnaire report from NIPH. This is not acknowledged, and seems to be a rough oversimplification of the assessment. As the MS kindly commented, this has been a thorough assessment based on a data package from the MAH with limitations and without having responded to all LoQs. All data that were available as been taking into consideration.

The MS proposes to closely monitor the issue in upcoming PSURs. We are of the opinion that currently there is enough data to conclude, and therefore does not agree upon postponing an assessment.

Comment from Member State (MS12)

Spontaneous reports as well as study data have major limitations, this also included the manuscript by Lill Trogstad et al. (2022, preprint and additional confidential analyses presented by No) "Increased occurrence of menstrual disturbances in 18- to 30-year-old women after COVID-19 vaccination"

Trogstad et al. reported an increased occurrence of menstrual disturbances, i.e. more heavy bleeding, prolonged bleeding, and short interval between menstruations among 5688 women aged 18-30 years.

Whereas the authors used the self-controlled case series (SCCS) design to perform the statistical analysis, which is adequate, the data were collected using a mobile phone questionnaire that was sent out once in late in October 2021 at a time when most of the participating women had already been vaccinated twice.

The method of data collection (cross-sectional survey) is associated with many limitations:

1) The survey was purely retrospective, although questions about menstruation before and after each Covid 19 vaccination were included. Thus, there is no "true" baseline. This would have been different if women had been questioned at different times, i.e. before and after each Covid-19 vaccination.

2) Depending on how long ago the vaccination(s) took place, women may remember different menstrual cycles (before/after the first covid-19 vaccination; before/after the second covid-19 vaccination) more or less well.

3) In autumn 2021, the topic of covid-19 vaccination and menstrual disorders was already discussed in the press and the topic was also picked up by social media. This may have consciously or unconsciously influenced the young women's response to the questionnaire.

Considering the above mentioned limitations, further studies (preferably prospective longitudinal ones) are needed to test the hypotheses generated within the scope of the cross-sectional surveys (Trogstad and others). In our view, in the absence of other clues to a signal (e.g. increased SMR in the observed-versus-expected analysis in spontaneous reporting), the evidence available up to this point is not sufficient to include menstrual disturbances as a side effect in the SmPC of Comirnaty.

PRAC Rapporteur's comment

Regarding the Trogstad study, the MS selects 3 limitations which are described. These limitations are acknowledged. Prospective longitudinal studies would indeed have been helpful, but taking into consideration the situation as of today with the mass vaccinations being over, recruitment to a prospective study would be challenging. Therefore we consider that prospective observational trials are not realistic. We therefore do not support the proposal to await further studies.

The MS mentions a lack of clues to a signal, such as an increased SMR in the observed-versus-expected-analysis in spontaneous reporting. It is not entirely clear if the MS suggests that such an analysis should be based on data provided by MAH in the form of an O/E-analysis, if so this is not supported giving the limitations of the O/E-analysis as pointed out in the assessor's comment box in the AR. We do not entirely agree that no clues to a signal exist, other sources of disproportionality analysis have been consulted: When consulting the WHO database Vigibase, the IC0.25 is disproportional, with a value of 2.7 (number of observed cases are 36 262, whereas number of expected cases are 5394. A positive value in the iC0.25 is the traditional statistical basis for signal detection at UMC). The PRR025 value is 10.8, the PRR value is 11.0, the ROR0,25 is 11.0 and the ROR

is 11.1 (as of 25 MAY 2022). EudraVigilance data show an ROR(-) of 11.32 as of 22 May 2022. O/E-analysis are a valuable tool in signal detection but less emphasis should be put on them when evaluating signals, especially a reaction like Heavy Menstrual Bleeding.

Comment from Member State (MS3)

We overall agree with both PRAC Rapporteurs that more data are needed to include heavy menstrual bleeding in section 4.8 of the product information. Specially, the cases with positive rechallenge should be investigated in detail. In addition, more studies would be necessary to reach firm conclusions, although we believe that a proper study design may be difficult in practice.

However, it is a fact that a large number of reports on heavy menstrual bleeding for both Comirnaty and Spikevax, some of them with positive rechallenge, have been reported and that available major studies (Torgstad and Carpensen), albeit limitations, points towards heavy menstrual bleeding.

Therefore, although it is unclear a causal relationship with the vaccine, this issue may create unnecessary worries in women, being normally mild and transitory disorders, we propose that a general warning in section 4.4 could be implemented to offer information about the temporal association with the vaccine as well as to state that the reported cases are mostly transitory and mild:

"Cases of heavy menstrual bleeding temporarily associated with <Comirnaty> <Spikevax> vaccination have been reported. Most of them are transient and mild in nature.

PRAC Rapporteur's comment

The MS suggest to include a text in section 4.4. This is not endorsed. Risks included in section 4.4 have at least a reasonable possibility of a causal association. Further, the guideline states that "Any adverse reactions described in this section or known to result from conditions mentioned here should also be included in section 4.8". Also, the criteria for inclusion in 4.4 are not considered fulfilled, as there is no specific advice to health care professional in order to reduce the risk. The guideline states that "Information on a specific risk should be given in section 4.4 only when the risk leads to a precaution for use or when healthcare professionals have to be warned of this risk". We therefore do not support including this in section 4.4, in order to comply with the SmPC Guideline, 2009. Further, regarding the wording of "transient and mild in nature": the current evaluation did not investigate the characteristics of the heavy menstrual bleeding such as its duration, and therefore we would be cautious to include information on severity and duration in the Product Information at this stage.

We appreciate the MS comment that there is a need for a PI update.

Comment from Member State (MS13)

Based on the totality of available data, we consider that there is currently insufficient evidence to support a possible causal association between heavy menstrual bleeding and Comirnaty vaccination.

All presented literature studies were limited due to recruitment of participants retrospectively, use of non-validated questionnaires, selection and recall bias. In the study by Trogstadt et al., while heavier than normal bleeding was identified as the change most associated with vaccination, the prevalence of any menstrual disturbance was 37.8% prior to vaccination, highlighting the high level of variation in normal cycles. A number of limitations were noted, including a lack of an unvaccinated control group

and a relatively low response rate (68.4%). We note that the authors highlight the key assumption of the SCCS model,[1] that the probability of being vaccinated is not affected by the occurrence of menstrual disturbances, but that it is not known whether menstrual disturbances may have influenced vaccination behaviour. Therefore, we consider that the identified studies do not provide sufficiently robust evidence that Comirnaty is associated with heavy menstrual bleeding.

We consider that additional, methodologically robust studies are required to investigate this potential association and to conclude on a causal relationship. We suggest that the MAH could be requested to discuss the feasibility of exploring the topic further in ongoing PASS studies.

Petersen I, Douglas I, Whitaker I. Self controlled case series methods: an alternative to standard epidemiological study designs. *BMJ* 2016;354:i4515

PRAC Rapporteur's comment

The Trogstad study was recruited prospectively, so the statement that all studies were retrospectively recruited is not endorsed.

We agree on the comment regarding the SCCS-analysis.

We are not of the opinion that a response rate of 68.2% is considered low. We consider it quite high seen in relation to the study type.

We do not consider that additional methodological robust studies such as randomized controlled trials are feasible in today's situation; please see the comment and justification addressed to DE.

Comment from Member State (MS4)

The PRAC Rapporteur proposition to update section 4.8 of the SmPC with 'Heavy period' is not endorsed.

In line with the comments of other MSs (MS12, MS10, MS11), we consider that the currently available scientific literature is inconclusive. Although the publication of Trogstad et al (2022) provides very valuable data, we support the analysis of MS12 regarding the limitations of the study.

However, considering the concern among women of childbearing age regarding menstrual disturbance, we would recommend the PRAC to consider the MS3 proposition for a general warning in section 4.4. It would be implemented for reassurance, stating that the reporting cases are mostly transitory and mild. The text we propose is amended as:

"Menstrual changes, such as heavier menstrual bleeding, temporarily associated with <Comirnaty> <Spikevax> vaccination have been reported. Most of them are transient and mild in nature"

PRAC Rapporteur's comment

We acknowledge the concern among women of childbearing age. However we do not support including the proposed text in section 4.4, in order to comply with the SmPC Guideline, 2009. Please see the more detailed comment addressed to MS3.

Comment from Member State (MS5)

MS5 does not fully agree to the conclusion and proposal from the Rapporteur assessment report.

First, MS5 endorses the rapporteur's assessment that several important information is missing such as the large number of ICSRs excluded from the analyses, the selection by the MAH of the serious and medically-confirmed serious cases while the review should have prioritised serious and/or medically confirmed cases. Moreoever, some information could be misleading such as MAH's interpretation of the criteria for classifying ICSRs according to the WHO-UMC causality assessment system.

Secondly, MS5 considers several of the published non-interventional studies mentioned in this report have some methodological limitations and unconclusive results. For the manuscript by Lill Trogstad et al., the study reports an increased occurrence of menstrual disturbances, i.e. more heavy bleeding, prolonged bleeding, and short interval between menstruations among 5,688 women aged 18-30 years. The used of the self-controlled case series design is adequate; however, this study has an important limitation which is the use of an unvalidated self-questionnaire concomitantly with media attention on this topic during the study.

However, MS5 considers that the available data cannot be ruled out a causal relationship between vaccination and heavy menstrual bleeding.

Awaiting for more comprehensive analyses on this important topic, MS5 considers that the update of the SmPC with "heavy menstrual bleeding" in section 4.8 should wait until the review of all missing information to be provided by the MAH and MS5 proposes a warning information to the public and healthcare professionals to be added to the in the section 4.4 of the SmPC.

If accepted for Cominarty, considering the uncertainties in the mechanism of action, the number of cases with both Spikevax and Comirnaty and heterologous vaccination patterns, this warning information should be also added in the SmPC of Spikevax.

In addition, MS5 proposes that the MAH provide the cumulative review and the PRAC assess this review within a next turn of this signal, and not to close the signal for now.

PRAC Rapporteur's comment

We acknowledge the comments regarding the limitations of the MAH's response. Although we agree that relevant data are missing from their analysis, we consider that the data available is sufficient to conclude that there is a reasonable possibility of a causal association. Therefore we do not support the proposal for an additional RSI with a cumulative review.

Regarding the inclusion of a warning statement in section 4.4.: this is not endorsed, please see the more detailed comment addressed to MS3.

Comment from Member State (MS8)

The LMS proposal to update section 4.8 of the SmPC with "heavy period" is not endorsed.

Although a numerical imbalance has been observed in clinical trials, the analysis of data conducted by the MAH is not sufficiently detailed and accurate to elucidate a possible causal association. Lack of information on clinical details of these cases are noted and we consider that further discussion is warranted.

We agree with LMS view that the MAH approach to case review is not completely supported and we considered that further details should be requested regarding overall number of informative and uninformative cases, age stratification, concomitant medications, risk factors and clinical history and WHO causality assessment, particularly for cases with rechallenge.

Overall, available literature on vaccine-associated menstrual disorders and particularly on heavy menstrual bleedings is scarce and limited with controversial results. Both studies by Trogstad et al. (including the very appreciated additional confidential analyses) and by Caspersen et al. have some limitations that affects the power of both studies, first of all the retrospective nature of data collection by phone survey. Moreover, it is unclear whether all risk factors for menstrual disorder and heavy periods have been considered as confounding factors.

We consider that further details are needed about the methodological limitations of the O/E analysis proposed by the MAH.

Therefore, we consider that the available data are not sufficient to support changes in PI at this stage. Further details are needed on the available data. Moreover, we propose to ask to the MAH whether this issue may be investigated in the ongoing PASS studies planned in the RMP or in other longitudinal studies.

PRAC Rapporteur's comment

The MS comments that further details of the cases should be requested, particularly for cases with positive rechallenge. We are of the opinion that these issues (more details on rechallenge cases, a more critical review of relevant cases) would not provide essential information at this stage. We are of the opinion that the currently available data is sufficient to establish at least a reasonable possible causal association in accordance with the SmPC guideline. Therefore we do not consider that an RSI is necessary.

The MS considers that further details are needed about the methodological limitations of the O/E-analysis. We are of the opinion that an O/E-analysis of "heavy menstrual bleeding" is of limited usefulness in the evaluation phase of a signal procedure.

Regarding the need for investigation in ongoing PASS studies, please see comment to MS12.

Comment from Member State (MS6)

We endorse the Rapporteur's view that despite the limitations of the Trogstad et al study and the spontaneous reporting data, together they indicate a potential causal relationship or at least a reasonable possibility of that, and endorse the Rapporteur's proposed recommendation. Further we suggest the use of the MedDRA PT 'heavy menstrual bleeding' instead of the LLT 'heavy period' in the SmPC section 4.8.

We support the Rapporteurs's view, that the MAH's case review is of limited value in the assessment of the signal, as a vast majority of the reports was excluded from the analysis (initially over 23 000 ICSRs, of which finally 71 cases were considered for further evaluation by the MAH).

Heavy menstrual bleeding is an ADR that seldomly leads to contacts with health care and thus is likely to be reported mostly by consumers. Since the diagnosis of heavy menstrual bleeding relies on the

anamnesis given by the patient, no medical confirmation is necessary for a reliable case, and the non-serious cases are as relevant for the causality consideration as the serious. We acknowledge that case-level analysis is not possible for all the cases given the number of reports. However, we do not agree with the approach that this leads to dismissing majority of the ICSRs when assessing the causal relationship.

Consumer reporting has also been promoted for a decade in the EU, and these reports cannot be excluded from safety analyses, at least when received in unforeseen quantities, although they are of limited quality. If they are considered of no value, the whole concept of consumer reporting should be re-evaluated.

PRAC Rapporteur's comment

The MS comment is appreciated. The reflections around consumer reporting are endorsed, and appreciated.

The MS proposes to include 'heavy menstrual bleeding' instead of the LLT 'heavy period'. This is endorsed, and the proposed recommendation has been updated accordingly.

Comment from Member State (MS2)

We can support the Signal PRAC Rapporteur conclusions to add heavy bleeding in the PI, however, before the final conclusion is made, additional data about cases from CTs and EV cases with positive rechallenge should be completed. Additionally, the MAH should provide the assessment of non-confirmed serious cases which was not made.

The analysis of CTs based on PTs revealed the numerical imbalance, 9 cases in vaccinated women vs. 3 cases in unvaccinated women. Unfortunately, as the Signal PRAC Rapporteur noted, the cases were not well structured by the MAH and exposure in women with childbearing potential was not provided either. Pre-existing medical history was described in 5 cases only (3 in vaccinated women, 2 in unvaccinated women). Therefore, the MAH should provide well structured, detailed description and assessment of these cases including an exposure of women of childbearing potential in CTs

Regarding the study of Trogstad, the self-controlled case series design is a suitable design for investigation of vaccines. The bias between a case and a control caused by inter-individual differences is minimized. Currently, when the exposure to vaccines is high in a general population, it could be expected that the populations of vaccinated and unvaccinated women are considerably different and comparison of these groups could be less suitable. The selection bias is minimized by random assorting of women from another ongoing population study. Therefore, inclusion of women was not driven by the existing menstrual disorders following vaccination. The recall bias was significantly solved by the app which was used by almost 60% of women. Even though menstrual disorders were observed in high percentage of women already before vaccination, RR increased after both doses of vaccine (1.9 (95% CI 1.69 - 2.13) after the first vaccine dose and 1.84 (1.66 - 2.03) after the second vaccine dose). The additional analyses were performed and the cases were stratified based on the pre-existing gynaecologist conditions or using of contraception which demonstrated higher RR also in women without any disease or contraception.

The results of this study are further strengthened by consistent results of another pre-print study (Caspersen et al), which has a similar design. The study was performed in girls of 12-15 years old. The occurrence of heavy menstrual bleeding was significantly higher in vaccinated girls with RR 1,61. Another study of Nguyen BT, Pang RD, Nelson AL, et al. which did not demonstrate higher risk of

menstrual disorders in relation to pandemic situation generally was also discussed and should be taken into consideration for this assessment.

We are aware that patients' self-reporting is not ideal for demonstrating a causal relationship, however because of the character of menstrual disorders we believe that higher percentage of confirmed cases cannot be expected, nor in the future. Waiting for better HCPs reported cases could mean that we never could conclude on this signal. The nature of this disorder should be taken into account. Majority of women do not visit their gynaecologist due to transient menstrual disorders only. However, in accordance with pharmacovigilance legislation, the patient cases should be taken into account during the assessment. The role of patient cases is significantly higher in situations, when causal relationship cannot be established based on medically confirmed cases because of the nature of condition. Even, if the case of transient heavier menstrual bleeding is medically confirmed, the confirmation is only based on what the woman told to the physician. The physician has very limited possibilities how to really medically confirm transient heavier menstrual bleeding and therefore, medical confirmation in this case in fact does not increase credibility of patients' reports.

The Signal PRAC Rapporteur also highlighted 186 cases in EV with a positive rechallenge. As these cases could play an important role, their detailed review would be very useful.

The Signal PRAC Rapporteur highlighted a poor quality of the MAH´s assessment, e.g. no discussion about backlog cases or underreporting, wrong causality assessment, not including serious non-confirmed cases. The MAH should provide updated assessment including serious non-confirmed cases and discussion about the backlog cases. Based on this more detailed assessment possible PI update should also be discussed.

PRAC Rapporteur's comment

The MS comment is appreciated, and we endorse the reflections around the challenges concerning this specific reaction when it comes to spontaneous reporting. We agree that the need for HCP reports are less relevant for heavy menstrual bleeding-reports, and that we should not wait for this.

The MS proposes an RSI, with more data (eg additional data about cases from CTs and EV cases with positive rechallenge and a MAH assessment of non-confirmed serious cases which was not made). We are of the opinion that currently there is enough data to conclude on an update of section 4.8 and therefore does not endorse a request for an RSI.

3.4. Updated rapporteur's proposed recommendation

Based on currently available evidence the PRAC Rapporteur considers that the SmPC/PIL should be updated with information regarding heavy menstrual bleeding. The MAH is asked to propose a frequency category.

The wording in of the proposed update to section 4.8 of the SmPC has been amended in accordance with the MS comments.

Text for SmPC

Section 4.8: Heavy menstrual bleeding.

Text for PIL

Section 4 (possible side effects): Heavy menstrual bleeding

3.5. Adopted PRAC recommendation

Having considered the data submitted by the Marketing Authorisation Holder (MAH), the PRAC concluded that the current evidence is insufficient to warrant an update to the product information at present.

The PRAC has agreed that the MAH of COVID-19 mRNA vaccine (nucleoside-modified) Comirnaty (BioNTech Manufacturing GmbH) should provide an updated cumulative review of heavy menstrual bleeding post-vaccination by 24/08/2022. The MAH should provide responses to the following list of questions:

List of Questions:

1. The MAH should discuss the possibility of further investigating the issue of heavy menstrual bleeding in a structured and prospective way in ongoing or subsequent clinical studies. The MAH should outline which possibilities have been explored.
2. The MAH should include in the updated review the following information on clinical trials:
    a. The exposure (patients' years) of female study participants of childbearing age in clinical trials.
    b. A detailed presentation (complete narrative and relevant case report form information) of cases of heavy menstrual bleeding in clinical trials.
3. The MAH should provide an updated case review, as per the below:
    a. All serious cases of heavy menstrual bleeding.
    b. All case reports of re-challenge of heavy menstrual bleedings with subsequent vaccination.
    c. The MAH should include in the case review also the cases in which there was concomitant use of other medicinal products (including concomitant use of contraceptives), or lack of information on medical history. Should confounders make a case ''not assessable''', a clear explanation should be provided.
    d. An assessment of the case reports according to UMC causality assessment criteria
    e. The MAH should justify the causality assessment, if "unlikely" or "non assessable /unclassifiable" is used.
4. In addition to the above-mentioned review which should include all case narratives, the MAH should provide a table as specified below. The table should include all serious and/or positive rechallenge cases and information including the categories shown in the separate columns. The MAH can suggest additional columns, if deemed useful. Data from this table should be easily extractable for assessment.

EudraVigilance case ID	Case narrative	Age	Time to onset	Duration	WHO-UMC causality category	Justification if causality is 'unlikely' or 'unassesable'	Confounded yes/no	Medically confirmed yes/no	Concomitant medication	Medical history	Positive rechallenge

The MAH should prioritize all ICSRs relating to this signal when handling the backlog of cases and report on the backlog at time of DLP.

The MAH should discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for changes to the relevant sections within this discussion.

The PRAC will assess this updated review within a 60 days' timetable.

4. 2nd assessment round

4.1. Assessment of additional data

4.1.1. Supplementary information from Trogstad et al

During the assessment of the MAH's response, the Norwegian Medicines Agency has received further additional data from Trogstad et.al. with supplementary analysis from the study "Trogstad, L. Increased Occurrence of Menstrual Disturbances in 18- to 30-Year-Old Women after COVID-19 Vaccination".

The paper is available as a preprint at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4324853

PRAC Rapporteur's comment

Trogstad et al. have performed additional analyses that were made available to the PRAC Rapporteur during the assessment of the response.

In addition to the findings already discussed in 3.1.1 and 3.2.3, an analysis stratified by reported previous menstrual regularity has been performed (Table 6 above). For women who reported that their cycles were always or usually regular*, the relative risk of experiencing heavy menstrual bleeding following COVID-19 vaccination was 2.00 (CI: 1.54-2.60) after dose 1 and 1.64 (1.33-2.01) after dose 2. This is consistent with the relative risk rates reported for all women, which were 1.90 and 1.84, respectively. These results demonstrate that the increased relative risk of HMB following vaccination is not driven by reported events in women who usually have irregular menstruation.

The number of women who report using a menstruation tracking 'app' was approximately 52 %. As discussed previously, this aid the responders in completing the questionnaires, thereby reducing recall bias.

Trogstad et al. have provided additional information on prevalence of menstrual irregularities stratified by vaccine type, which are consistent with the overall results discussed previously. Further, no differences are seen in the subgroup analysis based on length of vaccination interval (< 50 days, ≥ 50 days).

* In the questionnaire, participants were asked how regular their cycles were, and the reported numbers were: always regular (20.4 %), usually regular (53.3 %), usually irregular (13.0 %) and always irregular (6.3 %). Answers were missing for 7.0 %.

4.1.2. Assessment of MAH response to RfSI

Question 1

The MAH should discuss the possibility of further investigating the issue of heavy menstrual bleeding in a structured and prospective way in ongoing or subsequent clinical studies. The MAH should outline which possibilities have been explored.

MAH response to Question 1

Clinical Studies

Pfizer/BioNTech understand the reasoning behind this request, and it has been considered. To implement a clinical trial to investigate this issue would be challenging and the study design required would not be feasible (due to a number of factors including challenges in finding a large enough study population of females of childbearing age who have not received their primary series, the difficulty accurately evaluating HMB [eg, quantification of menses, quantification of what is a normal menses for the individual participant], follow up time that would be needed, determination of whether investigations would be required and which ones).

However, Pfizer/BioNTech propose that additional information could be collected from clinical trial participants reporting AEs of HMB. This could be achieved using an additional form within the CRF that could be completed by the site, and would collect required information including, previous menstrual history, use of hormonal contraception, etc. This would be implemented for any study within the C459 clinical development program including females of childbearing age with enrolment beginning in Q4 2022, to allow for time to incorporate this addition.

Non-Interventional Studies

Pfizer conducted a preliminary feasibility assessment to evaluate data sources suitable to conduct a PASS. The goal of the PASS would be to evaluate any potential association between the Pfizer-BioNTech COVID 19 vaccine and HMB in the EU and/or the US. As a part of this feasibility assessment, Pfizer conducted a preliminary review of data sources from the literature, held informational interviews with 3 academic researchers in the field, and evaluated 9 data sources (2 menstrual tracking software applications [‘apps’] with EU data; 1 menstrual tracking app with US only data; 4 US EMRs or claims data sources; and 2 US research cohorts). Key data elements assessed included region of data (EU or US prioritized), adequate capture of HMB, adequate capture of COVID 19 vaccination (including manufacturer), adequate capture of underlying medical conditions and other potential confounders that may impact menstrual cycle disorders, and a large sample size representative of the general population.

There is no consensus on a formal clinical definition of HMB. In the UK, HMB is defined by the National Institute for Health and Clinical Excellence as excessive menstrual blood loss, interfering with a woman’s physical, emotional, social, and/or material quality of life, and which can occur alone or in combination with other symptoms. Given the subjective nature of this outcome, a low proportion of all cases are likely to be brought to medical attention. Thus, the sensitivity of healthcare claims and/or medical record data alone to identify cases of HMB is expected to be low and were not further considered as a singular source of information.

Instead, menstrual tracking app data, completed by the patients themselves, may provide improved sensitivity to identify HMB across a large number of patients. Pfizer reviewed 3 menstrual tracking apps (2 with EU data; one with US only data) that collect self-reported information about menstrual flow volume and COVID 19 vaccination status in a subset of users. Menstrual bleeding volume is captured in the apps reviewed via 3 common categories: heavy, medium, and light.

Strengths of menstrual tracking app data include prospective data collection, capture of a wide range of menstrual cycle- related variables (eg, period dates, menstrual flow volume, menstrual- related pain), and large sample sizes of users from (depending on the app) the EU, the US, and other regions. Limitations of menstrual tracking app data include missing information (eg, some users may not record menstrual flow volume consistently or may miss recording a period entirely), self-reported COVID 19 vaccination resulting in potential missing information or incorrect dates, and a lack of detailed covariate and other medical history- related variables. Importantly, menstrual flow volume in the apps reviewed can only be collected via users self-reporting their menstrual flow volume categorically in the

app. Thus, quantitative volumetric measurements of HMB cannot be obtained. Rather, a potential future study could assess number of days in which the user tracks a 'heavy' flow among a subset of users regularly recording this data.

Linkage of menstrual tracking app data to an EMR data source may allow for improved ability to validate cases of HMB, identification of administratively-recorded COVID-19 vaccination information, the collection of comprehensive gynecologic history and potentially help characterise the clinical significance of HMB.

However, a comprehensive data source assessment is required to determine the feasibility of such a linkage in the EU and/or the US. To this end, Pfizer proposes to conduct a formal feasibility assessment of available data sources to evaluate a potential association between the Pfizer-BioNTech COVID-19 vaccine and HMB using linked menstrual tracking app data and EMR records in the EU and/or the US. Pfizer proposes to provide a timeline for completion of this feasibility assessment within 2 months.

PRAC Rapporteur's comment

Clinical studies

The MAH has considered the possibility of investigating the issue in clinical trials. Some major limitations that would confine the usefulness and feasibility of such studies are listed. These are overall endorsed, and the conclusion that such studies are not feasible is accepted.

It is agreed that examining HMB in non-vaccinated females of childbearing age in future clinical studies is unfeasible, as most have already been vaccinated with the primary series. Such studies could nevertheless detect newly arisen events and cases with positive rechallenge. This could be of value and add to the body of evidence, but prior vaccination status must be taken into account when interpreting data and could possibly confound the results, (rendering them less conclusive for the present signal evaluation). There is also a risk that women who experienced HMB during the primary series may be less willing to receive booster vaccination, potentially leading to selection bias towards those less sensitive to this ADR.

Further, the MAH highlights difficulties in accurately evaluating HMB. This reflects important limitations of the possibility of identifying HMB in any clinical study using customary study designs, including the pivotal studies with Comirnaty. To detect all cases with a heavier period, quantification of menstrual flow before and after vaccination should be performed and assessed in the context of the reported regularity of the individual participant's previous menstrual pattern. To examine the longevity of menstrual disorders and the extent of resolvement, a longer follow-up period would also be required.

As the general consensus is that menstrual irregularities are common, women in clinical studies experiencing less protruded changes may attribute them to normal variation, with only cases with a more severe outcome reported spontaneously as an adverse event. In the absence of quantitative measurements and/or specifically targeted reporting, there is a risk that events of heavy menstrual bleeding are insufficiently detected, potentially leading to underestimation. However, addressing this issue in coming studies is still appreciated. Additional studies may provide data assisting in estimating the incidence of HMB following COVID-19-vaccination. Obtaining such estimates based on spontaneous reports and observational studies are confined, and the incidences reported in the pivotal studies may be underestimated.

Regarding the additional form that is mentioned, we ask the MAH to consider including questions whether menstrual flow was increased following vaccination with the primary series. Additionally, baseline CRF data for WOCBP should include information on menstrual regularity and volume.

Non-interventional studies

The MAH has conducted a preliminary assessment of whether conducting non-interventional studies is feasible. No final proposal is given as part of the response, but some options are outlined and discussed. It is acknowledged that assessment of whether information from different data sources and registries may be linked is comprehensive. The MAH proposes to provide further details of the assessment within 2 months.

The options discussed focuses mainly on utilizing data collected through menstrual tracking applications (app) and electronic medical records (EMRs).

As amply pointed out by the MAH, given the nature of HMB, a low proportion of all cases are likely to be brought to medical attention. That the MAH seeks to address the extent of HMB through means where data from a large number of patients can be assessed is appreciated.

To accomplish this, the MAH has suggested to retrieve data from apps and has reviewed 3 different apps (2 from the EU and 1 from the US). There are no specific details on which apps have been investigated, which would have been expected and will be required in the final proposal. The discussion of strengths and limitations of menstrual tracking apps are endorsed. Data in apps are self-recorded and while the flow is only quantified in categories (reduced, normal, heavy), the apps aid the responders in answering, which helps reduce variability. The suggestion to analyse the number of days with 'heavy' flow is a reasonable approach. Additionally, the total number of days with recorded bleeding per cycle should also be analysed, as HMB may also include a longer cycle. A subgroup analysis of participants who have recorded their menstrual cycles consistently before and after vaccination could further strengthen the results.

It is argued that linking app data with data from an EMR can validate cases of HMB and COVID-19 vaccination status as well as provide information on medical history such as COVID-19 infection. While linking registries can provide a higher level of evidence, it is expected, as pointed out earlier, that a low number of HMB cases are expected to reach medical attention and therefore will not be registered in EMRs. Thus, filtering only cases that are recorded in an EMR is likely to exclude the majority of reports, counter-acting the purpose of utilizing such apps, which is to include a larger number of women. How the MAH plans to analyse the information retrieved is not specified and must include both app data and EMR data separately, in addition to an analysis of linked data. The MAH suggests including one EMR in the US in the studies. An explanation of why an EMR in the EU is not chosen for further feasibility assessment is not included, and the MAH is asked to reconsider including registries in the EU.

Challenges regarding privacy and data protection (GDPR) exist and how this will be accounted for must be discussed by the MAH. Conducting such a study requires explicit patient consent, which may represent a source of recruitment bias, even if data are already collected prospectively.

The approach the MAH suggests applying is overall in line with the study design of Trogstad et al, which shown an association between heavy menstrual bleeding and COVID-19 vaccination and was referred to in the first assessment round. As discussed in 3.1.3, participants in the Trogstad et al. study were already recruited as a part of an ongoing cohort and the authors study sought to mitigate limitations by applying a SCCS design and performing various stratified analysis. Trogstad et al. have performed additional analysis after the first assessment round of this signal evaluation, and this is included as supplementary information. Of notice, 52% of women in the study tracked their menses with an app (see section 4.1.1). Further, COVID-19 vaccination status was confirmed with data from the Norwegian Immunisation Registry (SYSYAK). Thus, the Trogstad study has already applied two means that the MAH highlights as useful to study HMB following vaccination.

Conclusion

The MAH's discussion and approach to how HMB following vaccination can be studied are overall endorsed. The MAH requests an additional two months to perform a feasibility assessment regarding non-interventional studies, which is accepted. Depending on PRAC's decision on the rapporteur's proposed recommendation, we suggest that the MAH consider including the following:

1) Baseline CRF data for women of childbearing potential should include information on menstruation regularity and volume.

2) Regarding, the design of non-interventional study utilizing apps and EMRs, the MAH is asked to include EMRs within the EU. This analysis should include both app data and EMRs data separately, as well as use of linked data.

In all, MAH's arguments in this section is overall in agreement with the position of the PRAC Rapporteur during the first round of assessment. As investigating HMB in clinical studies is unfeasible using a regular study design, emphasis should be made on data from spontaneous reports and well-designed observational studies, which the rapporteur finds to be the currently most feasible options to investigate an association of HMB and COVID-19 vaccination.

Question 2

The MAH should include in the updated review the following information on clinical trials:

a. The exposure (patients' years) of female study participants of childbearing age in clinical trials.

b. A detailed presentation (complete narrative and relevant case report form information) of cases of heavy menstrual bleeding in clinical trials.

MAH response to Question 2 a

The MAH reviewed the 2 largest placebo-controlled studies including participants within this age group (C4591001 and C4591031 SSA). The exposure of female participants of childbearing age to 30 µg of BNT162b2 vs Placebo for each study is 1610 PY vs 1720 PY for C4591001 and 270 PY vs 210 PY respectively. The MAH also added two tables with incidence rates in this age population.

Table 13. Incidence Rates of at Least 1 Adverse Event of HMB from Booster Vaccination to Unblinding Date, by System Organ Class and Preferred Term – Blinded Follow-up Period - Female Subjects 17-45 Years of Age -Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered)							
	BNT162b2 (30 µg) (Sub-Study A) (N[a] = 901, TE[b] = 2.7)				Placebo (Sub-Study A) (N[a] = 875, TE[b] = 2.1)			
	n[c]	% (95% CI[d])	IR (/100 PY[e])	(95% CI[f])	n[c]	% (95% CI[d]	IR (/100 PY[e])	(95% CI[f])
Any event	1	0.1 (0.0, 0.6)	0.4	(0.0, 2.0)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.8)
Reproductive system and breast disorders	1	0.1 (0.0, 0.6)	0.4	(0.0, 2.0)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.8)
Heavy menstrual bleeding	1	0.1 (0.0, 0.6)	0.4	(0.0, 2.0)	0	0.0 (0.0, 0.4)	0.0	(0.0, 1.8)

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. TE = total exposure time in 100 person-years (PYs) across all participants in the specified group. Exposure time for a participant is the time from booster vaccination to the end of blinded follow-up. This value is the denominator for the incidence rate calculations.
c. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any event.
d. 2-Sided CI based on Clopper-Pearson.
e. Incidence rate (IR) is calculated as number of participants reporting the event/total exposure time in 100 PYs across all participants in the specified group.
f. 2-Sided CI based on Poisson distribution.
Note: MedDRA (v25.0) coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 09JUN2022 (06:05) Source Data: adae Table Generation: 15AUG2022 (12:13)
Output File: ./nda2/C4591031_DMC10_23Jun2022_RR/adae_s131_6m_rel_saf

Table 14. Incidence Rates of at Least 1 Adverse Event of HMB from Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Female Subjects 17-45 Years of Age – Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered)					
	BNT162b2 (30 µg) (N[a] = 4156, TE[b] = 16.1)			Placebo (N[a] = 4451, TE[b] = 17.2)		
	n[c]	IR (/100 PY)[d]	(95% CI)[e]	n[c]	IR (/100 PY)[d]	(95% CI)[e]
Any event	3	0.2	(0.0, 0.5)	2	0.1	(0.0, 0.4)
Reproductive system and breast disorders	3	0.2	(0.0, 0.5)	2	0.1	(0.0, 0.4)
Heavy menstrual bleeding	3	0.2	(0.0, 0.5)	2	0.1	(0.0, 0.4)

a. N = number of subjects in the specified group.
b. TE = total exposure time in 100 person-years across all subjects in the specified group. Exposure time for a subject is the time from Dose 1 to the end of blinded follow-up. This value is the denominator for the incidence rate calculation.
c. n = Number of subjects reporting at least 1 occurrence of the specified event. For "any event," n = number of subjects reporting at least 1 occurrence of any event.
d. Incidence rate (IR) is calculated as number of subjects reporting the event/total exposure time in 100 person-years (PY) across all subjects in the specified group.
e. 2-sided CI based on Poisson distribution.
Note: MedDRA (v25.0) coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 22JUN2022 (09:38) Source Data: adae Output File: ./nda2/C4591001_DMC41_23Jun2022_RR/adae_s131_d1unb Date of Generation: 15AUG2022 (10:10)

PRAC Rapporteur's Comment:

The total number of female participants of childbearing age who received Comirnaty in the two trials were 5 057 participants. The PTY in the trials were 1880.

Table 13 and 14 demonstrates a numerical imbalance and a higher incidence rate of heavy menstrual bleeding in subjects receiving study drug than placebo, however the number of events is small.

MAH response to Question 2 b

The following unblinded, placebo-controlled clinical trials including women of childbearing age were reviewed for reported AEs with the MedDRA preferred term Heavy menstrual bleeding:

-C4591001 (A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals).

-C4591031 Sub-study A (A Phase 3 Randomized, Placebo-Controlled, Observer-Blind Sub-study to Evaluate the Safety, Tolerability, and Efficacy of a Booster Dose of BNT162b2).

Within the blinded phase/follow up period of both studies, (defined as from first vaccine received to unblinding date), out of a total of 5057 participants exposed to BNT162b2 and 5326 exposed to placebo, 6 AEs of HMB were reported. Of these 6 AEs reported 1 event was considered serious, due to hospitalisation, (narrative included below) and 2 events were considered related to the study intervention by the investigator. After unblinding, it was confirmed that 4 events occurred in participants who had received BNT162b2 and 2 events occurred in those who had received placebo. The age range of women affected was 29-41 years, the earliest event start date was 7 days post vaccination and the latest was 115 days post vaccination (mean days post vaccination = 35.5), with an event duration of 6-143 days (mean duration = 39.6 days, 1 event end date was unknown).

During the open label phase of both studies, further 6 AEs of HMB were reported (all within Study C4591001) of which 1 event was considered serious, due to hospitalisation, (narrative included below) and 1 event was considered related to the study intervention. Four of these events occurred after receiving the first booster vaccination of BNT162b2 30 µg.

Two cases were reported to be SAEs and narratives were available:

Case 1 (blinded phase): An adult female participant with a pertinent past medical history of caesarean section (3 events) and menorrhagia which started approx. 9 months and a half before first dose of Comirnaty, and lasted for 18 months, for which she received tranexamic acid (Lysteda). She was vaccinated with dose 1, and dose 2 19 days later, both confirmed as active BNT162b2 30µg. Booster dose was given approx. 6 months and a half after dose 1. Approx. 4 months and a half after dose 1, the participant experienced worsening of menorrhagia which required a visit to her physician's office and an emergency room visit that resulted in hospitalisation for 1 day. The clinical course was as follows: Worsening of menorrhagia approx. 4 months and a half after dose 1 for which the participant was admitted to hospital and underwent a hysterectomy approx. 7 months and a half after dose 1 and was discharged the following day. No relevant tests were reported. The investigator considered there was not a reasonable possibility that the event worsening of menorrhagia was related to the study intervention.

Case 2 (open label phase): An adult female participant with no pertinent past medical history. Vaccination 1: placebo, vaccination 2: 20 days after dose 1(placebo), vaccination 3: approx. 5 months and a half after dose 1 (active drug), vaccination 4: approx. 8 months and a half after dose 1 (active drug). The patient contacted her clinic to report that that she had started having menorrhagia 4 months after dose 4 and her obstetrics and gynaecology physician could not locate the cause of the bleeding. She was hospitalised 6 months after dose 4, for one day for the menorrhagia and started oral doxycycline at 100 mg twice a day during hospitalisation (ongoing), (as doxycycline is not a standard treatment for menorrhagia the reason for the prescription is not confirmed). The participant reported that due to the menorrhagia she had a laparoscopic hysterectomy 2 weeks after hospitalisation. She

was prescribed hydrocodone/acetaminophen 5/325mg orally as needed for post-surgical pain. The investigator considered there was not a possibility that the event "menorrhagia" was related to study intervention.

PRAC Rapporteur's Comment:

8 events of HMB occurred following active drug, and 4 following placebo. Of these, 3 events were considered related by the study investigator.

The MAH has not provided narratives of all cases of heavy menstrual bleeding. From a total of 8 cases of HMB following active drug, only 2 had case narratives (those considered SAEs).

The MAH provided a line listing of all 12 HMB cases, however it is not possible to determine whether vaccine or placebo was given for some patients

The MAH summarised their findings in the response (in text) so it is possible to detect how many were following placebo vs active drug, but the MAH is requested not to submit data that are impossible to interpret.

2.3. Question 3

The MAH should provide an updated case review, as per the below:

a. All serious cases of heavy menstrual bleeding.

b. All case reports of re-challenge of heavy menstrual bleedings with subsequent vaccination.

c. The MAH should include in the case review also the cases in which there was concomitant use of other medicinal products (including concomitant use of contraceptives), or lack of information on medical history. Should confounders make a case "not assessable"', a clear explanation should be provided.

d. An assessment of the case reports according to UMC causality assessment criteria

e. The MAH should justify the causality assessment, if "unlikely" or "non assessable/unclassifiable" is used.

MAH response to Question 3a

A total of 7824 serious cases containing the PT Heavy menstrual bleeding were identified in the search. Of the 7824 cases, 7788 (99.5%) cases were spontaneous, 24 (0.3%) cases were solicited, and 12 (0.2%) cases were from clinical studies. Of the serious cases, 655 cases were medically confirmed.

Age ranged from 10 years to 84 years. Mean and median age were 35 years (n = 6864).

Ages	Number of cases	Percentage
Less than or equal to 17 years	148	1.9 %
18 - 30 years	2064	26.4 %
31 - 50 years	4255	54.4 %
51 - 64 years	391	5.0 %
65 - 74 years	6	0.1 %
More than or equal to 75 years	1	0.0 %
Unknown	959	12.3 %

The cases were analysed to identify confounders or potential alternative causes of HMB such as anxiety, depression, blood coagulopathies, anaemias, malignancies, hypothalamic or pituitary disorders, endocrine gland disorders, gynaecological disorders, tobacco use, COVID-19 infection, autoimmune, and other diseases for which there is medical literature describing their potential impact on menstruation and bleeding risks. This review yielded **2446 cases noted as confounded**.

Another analysis was performed to identify those containing concomitant or co-suspect medications indicating a potential baseline of, or risk factors for, HMB such as antidepressant use and antianxiety medications, iron and thyroid supplements, antidiabetics and insulins, tumour necrosis factor inhibitors, tranexamic acid, etc. since these treat diseases linked to menstrual abnormalities and blood coagulopathies. Also identified were cases with concomitant hormone use and gonadal steroids (other than contraceptives) and other medications that might be associated with menstrual abnormalities and bleeding as an ADR such as selective estrogen/progesterone receptor modulators, aromatase inhibitors, and anticoagulants. This review yielded **801 cases noted as confounded.**

In total, there were **2659** serious cases in which diseases and/or other medications provide plausible explanations for HMB, rendering these cases as **"unlikely"** to be caused by the vaccine, using the WHO-UMC causality assessment categories as requested.

Of the remaining 5156 cases, the MAH categorized **3038** as "**unclassifiable/unclassifie**d". The explanation for this categorization is that key case information was insufficient for a proper causal assessment; key information being clinical outcome, dose number, and time to onset (either not provided or outside of a plausible 0-30 days latency window from time of vaccination)

The MAH then focused on the cases in which HMB was a serious event. HMB occurred after dose 1 for 1141 events, after dose 2 for 645 events, after dose 3 for 190 events. There were no HMB events reported after dose 4.

Outcomes were resolved/resolving for 750 cases, not resolved for 1147; resolved with sequelae for 54 cases; and unknown for 38 cases.

The most frequently reported latency for HMB events was day 1 (for 236), day 0 (for 211) and day 3 for 117).

The MAH divided their review into co-reported events or not. For those with a co-reported event (151 cases), the most frequent PTs were listed below

PT	Number of Cases
Dysmenorrhoea	595
Menstruation irregular	279
Fatigue	223
Menstrual disorder	201
Headache	161
Menstruation delayed	119
Immunisation	112
Polymenorrhoea	108
Nausea	102
Inappropriate schedule of product administration	101
Off label use	101
Pain	99
Dizziness	91
Muscle spasms	91
Interchange of vaccine products	86
Haemorrhage	83

The MAH states that in **81** cases the co-reported events suggested a potential **alternative etiology**: spontaneous abortion, postmenopausal haemorrhage, pulmonary embolism, thrombocytopenias and thrombosis/phlebitis disorders.

The remaining 1440 cases were searched for reports of hospitalisation and 21 cases were returned. Of the 21 cases, 11 cases provided little clinical detail, but 10 cases reported low haemoglobin, haematocrit and/or anaemia, 8 of which reported that treatment was required. 9 of the 21 cases were medically confirmed.

In the response, the MAH described ten cases of hospitalisation:

Case No and narrative	MAH's assessment	PRAC Rapp Comment
Case 1: An adult experienced a miscarriage. On a medical appointment less than one month later the miscarriage was resolved, something was left to expel at next menstruation 3-4 weeks later. She was vaccinated with her Dose 1 of BNT162b2 more than one month after the miscarriage. 5 days later, the patient experienced vaginal bleeding that she thought was menstruation; however, the next day she was hospitalised due to clots, intense bleeding and "the rupture of a vessel causing anaemia" Uterine aspiration was performed and an intrauterine catheter was placed. She was treated with tranexamic acid, paracetamol, lactase, ketorolac, tramadol, oxytocin, cefazolin during her 1 day of hospitalisation. Her haemoglobin was 9 g/dL upon discharge. She was recovering with treatment including iron, ethinylestradiol and gestodene	Unlikely causality based on recent miscarriage history	The criteria that may render the classification 'Unlikely' are firstly the time relationship is improbable (with the knowledge at the time), and/or another explanation is more likely. The PRAC Rapporteur disagrees with the causality classification.
Case 2: Ten days after the Dose 2 of BNT162b2, an adult patient presented to the hospital with heavy vaginal bleeding for the preceding 5 days. The patient had a history of a regular cycle with very mild menorrhagia on Day 1 but otherwise	Possible.	

no major history of heavy bleeding. The patient was hospitalised for heavy vaginal bleeding with clots and flooding with a haemoglobin of 6.3 g/dL on arrival. She was treated with Tranexamic acid IV 1 g and Provera 10 mg daily. The patient was transfused 1 unit of red cells. She was discharged after 2 days with a stable haemoglobin of 9.6 g/dL and her bleeding had greatly lessened. A hysteroscopy was performed approximately 1 month later which showed a normal cavity. Histology showed benign endometrium. A Mirena coil was inserted and HMB was recovering.		
Case 3: A girl was vaccinated with her Dose 2 of BNT162b2 and the next days experienced long menstruation, different from the menstruations since menarche on a monthly basis over the last 2 years. She presented to the emergency room 21 days later with asthenia, headache, and a haemoglobin of 6.2 g/dL which required urgent transfusion. She was recovering after treatment with tranexamic acid, folic acid, Vitamin B12, and iron.	Unlikely. Immature hormonal cascade controlling menstruation during adolescence.	The menstruation had been stable for the last 2 years, and it is not agreed that the causality is "unlikely".
Case 4: An adult was vaccinated with her Dose 1 of BNT162b2 and experienced "a lot of blood loss" during the next menstruation, felt very tired and unwell. Dates were unspecified. Eighteen days after Dose 2, she was hospitalised for malaise, menstrual flow excessive, syncope, a serious case of anaemia by blood test, spots before eyes, exercise tolerance decreased and fatigue. She was treated with iron and recovering.	Unlikely. Immature hormonal cascade controlling menstruation during adolescence.	The patient reported events following both doses, and is a case of positive rechallenge. The dismissal of the case is disagreed upon. The information in the case does not fulfil the criteria for classification of "unlikely".
Case 5: An adult experienced severe menstruation like bleeding, 16 days after the Dose 2 of BNT162b2 and haemoglobin "decreased a little" resulting in hospitalisation. The patient underwent lab tests and procedures which included lower abdomen scan: results not specified, blood test multiple: results not specified, haemoglobin: has decreased a little, smear test: negative. The patient was treated with IUCD and was recovering	Unassessable as case lacked dates and history. Details do not rule out perimenopause as alternate causality.	The case includes information on TTO (16 days), and it is not clear why the exact date of the event is necessary for the MAH to be able to assess the case.". The guidance document from WHO-UMC (Annex III) states that "when the information in a report is incomplete or contradictory and cannot be complemented or verified, the verdict is 'Unclassifiable' and the MAH's conclusion is not aligned with this. It is not agreed that the case is "unassessable".
Case 6: Six days after the Dose 1 of BNT162b2, an adult patient experienced pyrexia and menorrhagia which required hospitalisation. Lab tests included haemoglobin 7.4 g/dL, iron 12 µg/dL, CRP 5.6 mg/dL. The patient recovered	Unassessable as case lacked dates and history. Details do not rule out perimenopause as alternate causality.	The case includes information on TTO (six days), and it is not clear why the exact calendar date of the event is necessary for the MAH to be able to assess the case. It is not agreed that the case is "unassessable".

Case 7: An adult had not had her period for 1 year. She was vaccinated with her Dose 2 of BNT162b2 and on that day experienced HMB for 9 days, dizziness, and falling haemoglobin, measured at 9.2 g/dL. She was hospitalised and the outcome was unknown.	Unlikely. Hormonal imbalances during perimenopause may result in heavy and irregular bleeding	The patient had not had her period for 1 year, hence she is not in perimenopause, but in menopause. This is therefore a case of postmenopausal bleeding and should not be dismissed.
Case 8 Two days after her Dose 1 of BNT162b2, an adult patient experienced HMB from the uterus needing blood transfusion of 2 units. She did not have similar HMBs previously. Primary suspected cause was anovulatory bleeding. The patient underwent lab tests and procedures which included Haemoglobin: 6.7 g/dL (12 days post vaccination) and 8.9 g/dL (13 days post vaccination). She was treated with tranexamic acid, norethisterone and given iron supplementation and HMB was recovering.	Unlikely. Hormonal imbalances during perimenopause may result in heavy and irregular bleeding.	The reporter is aware of the patient's age (and hormonal status) when submitting the report. The MAH's classification of the case as unlikely due to perimenopause is not supported. Also, the case mentions that she has not had similar heavy bleedings previously. It is not agreed that the correct causality assessment category is "unlikely".
Case 9: An adult patient had her first period 13 days after her first BNT162b2 vaccination. The bleeding did not subside, and she was admitted to hospital for immediate help 2 weeks after the first day of her period with severe bleeding anaemia. The patient had haemoglobin of 4.0 g/dL and received 4 blood transfusions and 3 bags of fresh frozen plasma. Ultrasound scan showed blood in the uterus with thick and even mucous membrane. She was examined for coagulation disorders with normal findings and had recovered.	Unlikely. Immature hormonal cascade controlling menstruation during adolescence.	The reporter is aware of the patient's age (and hormonal status) when submitting the report. The MAHs classification of the case as unlikely due to immature hormonal cascade seems to be a default approach based on the patient's age and is therefore not supported.
Case 10: An adult female received Dose 3 on Day 3 of period. The Dose 1 and Dose 2 of BNT162b2 vaccine were received on unknown dates. Medical history, and concomitant medications were not reported. She experienced fatigue, HMB, asthenia, dizziness, and muscular weakness starting on the day of vaccination and the next day. She experienced syncope, vomiting, tinnitus and headache on an unknown date. She was admitted to the hospital on 1 week after dose 3, haemoglobin was "6 points," she received blood transfusion and another unknown medication.3 days later the patient didn't improve and was transferred to another hospital. At the time of the report, the outcomes of the events were not resolved. No other information was present in this case.	Possible.	

Of the last **1419 cases in which hospitalisation was not reported**, **1295 cases provided little clinical detai**l, but 24 cases reported low haemoglobin, haematocrit and/or anaemia, 12 of which reported that treatment was required. The clinical outcome for HMB event in the 24 cases was

resolved/resolving for 5 cases, resolved with sequelae for 2 cases and not resolved for 17 cases. Causality was assessed and these cases were included in Appendix 2. A line listing of these 24 cases were submitted on 2 September 2022 after a request for further information.

82 of these 1419 cases were medically confirmed.

Concomitant use of contraceptives was reported in 92 cases; 22 of these 92 cases reported indication for contraceptive as "contraception"/other indication (e.g., pain), or unknown and reported that HMB after the vaccination was not normal as compared to their usual menstruation flow (normally they had no or light periods while on contraception, etc.).

The rest of the cases reporting HMB as an SAE (284 of 1805), reported HMB as the only event (no co-reported events). Nine of the cases reported hospitalisation; but none of them reported low haemoglobin, low haematocrit, and/or anaemia. The causality assessment for these 9 cases is provided in Appendix 2. None of the last 275 cases that did not result in hospitalisation reported low haemoglobin, haematocrit, and/or anaemia. Twenty-one of the 284 cases were medically confirmed. Out of 284 cases, 23 reported concomitant use of contraceptive; 12 of these 23 cases reported contraception as the indication (vs. treatment for menstrual irregularities) and that HMB after vaccination was not normal compared to their menstrual history (either they had no periods while on contraception, their periods were light, etc.)

***PRAC Rapporteur's Comment**:*

Methodology and causality assessments:

The MAH has selected 10 cases from a total of 7824 serious cases containing the PT HMB. This selection is considered extremely small, and the MAH's methodology is questioned, as it was in the first round of assessment of the response.

3038 cases were categorized as "**unclassifiable/unclassified**" due to key case information being insufficient. The cases fulfil at least the minimum requirements for reporting and are all valid ICSRs There is no established definition of "key case information" in the evaluation of spontaneous reports, and this seem to be based on subjective judgement.

"The use of the WHO-UMC system for standardised case causality assessment" states "when the information in a report is incomplete or contradictory and cannot be complemented or verified, the verdict is 'Unclassifiable'" The MAH's causality assessment is not aligned with the UMC guidance.

The PRAC rapporteur has looked into a random selection of these cases, please see examples below, and according to our judgement they do contain key information: information on the patient, information on the event, information on the suspect drug. It is not agreed that these are "unclassifiable/unclassified" per the WHO-UMC causality criteria. It is not agreed that "outcome" and "dose number" is key information, and these cases should not per default be dismissed

2659 serious cases were categorised as "**unlikely**" by the MAH due to concomitant disease and/or other medication that in their opinion provide plausible explanations for HMB. In the WHO-UMC-document mentioned above (appendix III), the following is stated: The criteria that may render the connection 'Unlikely' are firstly the time relationship is improbable (with the knowledge at the time), and/or another explanation is more likely The MAH's utilisation of "unlikely" on 1/3 of all reported cases seems overly conservative, and the MAH has not justified that the alternative explanations are more likely than the vaccine.

2446 cases were noted as **confounded**. A case with a co-morbidity which might affect menstruation is not per default confounded. Each individual case has to be assessed in order to establish whether the co-morbidity has been stable for a long period of time and whether it is the most likely causative factor or rather a possible contributing factor.

801 cases were dismissed because the patient had been treated with **medications** indicating a potential baseline of, or risk factors for, HMB. This methodology is not supported. Each individual case has to be assessed in order to establish whether the co-medication has been ongoing for a long period of time, i.e. is considered stable and not a likely causative factor.

Hospitalisations – case overview

It is not clear why the MAH has removed **1419 from a total of 1440** (98,5%) serious reports, because the patient was not hospitalised. *This criterion* was not mentioned in the list of questions, and the dismissal of these cases is not accepted. Heavy menstrual bleeding rarely warrants hospital admission, and not hospitalised patients should not per default have been excluded.

Hospitalisations – review of presented cases

The MAH presented 10 cases out of 21 cases of hospitalisation. We find that the MAH's assessment of these cases has applied a very stringent/conservative approach. For instance, case 3 where a girl experienced heavy menstrual bleeding and went to the emergency room, was classified as "unlikely" by the MAH due to "immature hormonal cascade". The report states however that the girl's menstruation had been stable for the past two years. The same classification as "unlikely" with the justification of an "immature hormonal cascade" was applied to case 4 regarding a girl who was admitted to hospital after experiencing a "serious case of anaemia". The girl experienced heavy menstrual bleeding following both dose 1 and dose 2 and is therefore a case of positive rechallenge, and it is not agreed that the case should be assessed as "unlikely**". This case was not detected as a positive rechallenge case by the MAH,** as it is not marked as a potential positive rechallenge case in appendix 2. The PRAC Rapporteur therefore questions whether the MAH has correctly evaluated/detected cases with positive rechallenge information. Please see comment on question 3c.

Hospitalisations – review of cases categorised by the MAH as having little clinical detail:

The ID numbers of the 11 cases with hospitalised patients which the MAH stated had little clinical detail and therefore dismissed, was submitted to the PRAC rapporteur on 2 September 2022 per, as they were not possible to retrieve in the original response.

A short summary of the cases is presented below. Not all information available is provided, but relevant information is included, in order to secondary assess whether they have little clinical detail (as stated by the MAH) or not.

Case 1: An adult received second dose of Comirnaty. Medical history included lactation decreased. Patient had last menstrual period 3 months after second dose of Comirnaty. First dose received 3 months prior to second dose. She experienced vomiting, fever, neck pain, shaking inside, heavy menstrual bleeding, rash, headache, chest pain starting on the same day when she received the second dose of Comirnaty. She had several visits to Accident & Emergency (A&E) with pain, referred to physician for neck and shoulder pain after vaccine. Dates are somewhat conflicting as regards last menstrual period and vaccination.

Case 2: An adult taking a birth control pill which is a continuous pill, and had almost no menstruation. Vaccinated with dose no. 2. TTO 7 days. The bleeding 7 days later was so heavy she had to empty the menstrual cup every half hour of a whole night. Strong heart palpitations from climbing stairs. She was

admitted to hospital and prescribed tranexamic acid500mg for blood clotting. Blood test (plate count) 10 days after dose 2 was 232.

Case 3: Age 30-39 received Comirnaty as dose 2, reported of anaemia and heavy menstrual bleeding 5 days later. A very detailed narrative is included in the report. The patient had been bleeding for a month since her second vaccine; had been to accident and emergency (A&E); booked an ultrasound, blood tests and nothing can be found. She experienced heavy bleeding outside periods. The patient had no history of heavy periods, or of conditions which can cause heavy periods, e.g., fibroids, polycystic ovaries, endometriosis. The patient had no history of any other period related problems e.g., irregular periods. The patient had no history of bleeding disorders or low blood platelets. The patient had no history of long-term medical conditions or take any regular medication. The patient had no similar reaction to any other vaccine or medicine. She has neither been diagnosed with COVID-19 nor had a suspected COVID-19 infection.

Case 4: An adult received, second dose of Comirnaty 2 months after the first dose. It was reported that the bleeding occurred after the 1st and 2nd vaccine. The patient experienced heavy menstrual bleeding with blood clots and reported that period started 5 days early, starting 7 days after second dose of Comirnaty and a low blood count of 32. The period went on for 15 days, and patient sought help on day 8. 2 days later admitted with a low blood count. Treated with noretisterone and bleeding stopped. Information on previous cycles: usually her cycles are regular and lasts only 5 days: She did not have any other unexpected bleeding at the same time, e.g., nose bleeds. Not any history of conditions which can cause heavy periods e.g., fibroids, polycystic ovaries, endometriosis etc. Negative test for covid-19.

This case is a positive rechallenge case, **but not included in the MAHs list of positive rechallenge cases**. Case 5: An adult vaccinated with Comirnaty. Medical history includes hypercholesterolaemia. Also reported tenderness in arms and chest. Reported very heavy bleeding causing hospitalisation from the month of vaccination with Comirnaty. Menstruation had not been present since 6 months (unknown whether before or after vaccination). ECG and blood tests taken, results unknown.

Case 6: An adult vaccinated with Comirnaty as dose 2. TTO 20 days. She reports a severe headache, and she took sick leave from her work (in a hospital) as she was unable to safety deliver care. The report includes a detailed description of the events. The patient reports of her period starting 5 days early, and a substantially heavier flow. She had very heavy menstrual bleeding. Negative test for COVID-19.

Case 7: An adult received Comirnaty as dose 1, comorbidities were asthma and allergy. She experienced endometrial hyperplasia, heavy menstrual bleeding. Report states that events might coincide with menopause but did not have this prior to the vaccine. Report includes information on biopsy of uterine polyp, blood tests (low iron, increased reticulocytes and basolycytes). Patient also suffered from vaccination site erythema and paraesthesia (tingling in the whole body and the feeling of tingling in the eyes and jaws). She was examined in allergy clinic with unknown results. Neurological examination showed nothing abnormal. Height and weight are reported.

Case 8: An adult received Comirnaty on 6 Sept 2021 as dose 1. Since the vaccine she has heart flutters, chest pain, shortness of breath around menstrual cycle. "Been fobbed off told it's anxiety but bloods come back". Somewhat difficult narrative to interpret.

Case 9: An adult received Comirnaty as dose 1. The report states that heavy periods started in the following day of the vaccine. Blood flow much heavier than expected – only for the first day. Seizures two days after the vaccine, 2 small seizures (around one minute each), CT scan result were normal and blood exams only resulted in high white blood cells count. Patient has not tested positive for covid-

19 since having the vaccine. The patient underwent lab tests and procedures which included covid-19 virus test (negative result) 23 days before dose 1, CT scan normal on unknown date.

Case 10: A girl received first dose Comirnaty. Date of last menstrual period was approx. 3 months after first dose. The patient reported that on an unknown date heart rate was abnormally quicker. 9 days after vaccination the patient experienced heavy periods. The patient was admitted to accident and emergency due to the amount of blood lost due to period. The patient had intravenous drip. Covid-19 virus test was negative. The patient underwent heart rate test, and the result was abnormally quicker. The patient underwent ultrasound scan, internal scan, blood tests and urine samples; results were unknown.

Case 11: An adult received Comirnaty. Relevant medical history includes thalassemia beta, unknown if ongoing, and allergy to peanuts. The patient experienced heavy menstrual bleed requiring hospitalisation for two days and characterized as life threatening 8 days after receiving Comirnaty. The event was reported as "severe menorrhagia on a background of fibroids". Haemoglobin 64. SARS-Cov-2-test negative 6 months after receiving Comirnaty. Nasal swab 7 days later negative. Therapeutic measures were blood transfusion, tranexamid acids, intravenous iron.

We disagree with the MAH in discarding all these cases with the justification that they contain little information. We consider that the cases contain enough information to provide valuable input for the assessment of the signal in question, and the bar for what is regarded as information needed in an ICSR is set unrealistically high. One of the cases is a positive rechallenge case and hence is particularly valuable, yet this case has been left out from the MAH's review.

LOW HAEMOGLOBIN

The MAH stated that there were 24 cases reported low haemoglobin, haematocrit and/or anaemia, 12 of which reported that treatment was required. The MAH did not provide IDs of these cases, and this was therefore requested and provided on 2 Sept. The 24 cases have been reviewed by the PRAC Rapporteur. There are several well described cases of prolonged bleeding. Some of them have Hb measured in the spectrum 8 – 13.

Question 3b Response – Cases of positive rechallenge

Methodology: Cases of potential rechallenge were identified by searching for cases with the PT heavy menstrual bleeding and more than 1 suspect dose of BNT162b2 coded within the case. This search did not automatically exclude cases based on the clinical course between doses (e.g., cases in which treatment for HMB was received between doses or cases in which the event continued between doses). It also did not exclude cases reporting rechallenge associated with more than 1 dose of COVID-19 vaccine in an individual. There were 480 serious cases and 591 non-serious cases, **1071 in total**.

The potential rechallenge cases were analysed to identify patients with a medical and/or familial history of confounders – this yielded 281 cases noted as confounded.

Another analysis identified those containing concomitant or co-suspect medications which may indicate that the patient had a risk of HMB such as antidepressant and antianxiety medication, iron and thyroid supplements, antidiabetics and insulins etc. This yielded 112 cases considered confounded by the MAH.

315 cases were considered **"unlikely**" by the MAH.

584 were considered **"unclassifiable/unclassified**" because key case information was missing, such as clinical outcome, dose number, and time to onset (either not provided or outside of a plausible 0-30 days latency window from time of vaccination).

The remaining 172 cases of potential rechallenge were assessed.

43 of the cases described distinct episodes of HMB within a reasonable timeframe following more than 1 dose without specified treatment provided for the event. 29 were unclassifiable, 4 were unlikely and 10 were possibly causally related.

PRAC Rapporteur's Comment:

The MAH did not provide information that made it possible to retrieve the positive rechallenge cases for a secondary assessment, despite it being specified in the original LoQ. The MAH was therefore requested to provide information that made this feasible. The MAH responded to this and added a column to one of the sheet tabs in Appendix 2 with the criterion 'hospitalisation Yes/No/NA'. However, the case narratives remained in a different sheet tab and a summary of narratives of all positive rechallenge cases were therefore not provided by the MAH.

The MAH's methodology for identifying cases of positive rechallenge was to search for cases with more than one dose of BNT162b2 coded in the case. The MAH has apparently not searched for cases in which the positive rechallenge field in the ICSR has been populated with "yes". In these cases, the coding of positive rechallenge may be based on information provided in the narrative, and two doses of the suspected drug is not always coded. Therefore, it is possible that several cases of positive rechallenge has not been taken into consideration in the MAH's review, and the number of cases with positive rechallenge is higher than the number presented by the MAH.

The PRAC Rapporteur has reviewed all of the 129 cases categorized as 'not a rechallenge case' by the MAH and agree that the majority of these do not contain information on reactions following both doses, or they are describing a reaction following dose 1 that persists and continues after dose 2. However, in nine of the dismissed cases there is information in the case narrative indicating a positive rechallenge, such as statements like "this happened following both doses"

Overall, the MAH has deleted 899 from a total of 1071 potential positive rechallenge cases because they were considered "unlikely" or "unclassifiable". The PRAC Rapporteur does not endorse the MAH's methodology and their application of the causality criteria, as discussed elsewhere in the report (under question 3e)

There are 43 cases of positive rechallenge included in the response, but due to the issues regarding the MAH's dismissal of cases, the number of positive rechallenge cases is unknown.

Question 3c - The MAH should include in the case review also the cases in which there was concomitant use of other medicinal products (including concomitant use of contraceptives), or lack of information on medical history. Should confounders make a case "not assessable"', a clear explanation should be provided

MAH's response:

Cases in which there was concomitant use of other medicinal products (including concomitant use of contraceptives) that was relevant to the event HMB, or lack of information on medical history were included in the analysis and responses provided for questions 3a and 2b. The MAH states that the table requested in Question 4 and in Appendix 2 also includes this information.

PRAC Rapporteur's comment:

The specification of question 3 (the MAH should include cases in which there was concomitant use of other medicinal products etc) was given because the MAH in their first response eliminated the majority of the ICSRs from review: in total 99.94% of reports were dismissed and the Rapporteur disagreed with the approach and methodology. In the opinion of the Rapporteur, it was considered important to emphasize that the MAH should include these cases in their review.

3 d) An assessment of the case reports according to UMC causality assessment criteria

The MAH assessed the 7738 most clinically relevant cases (out of 8418 total cases) using the UMC causality criteria within responses provided for question 3a and 3b

3 e) The MAH should justify the causality assessment, if "unlikely" or "non assessable/unclassifiable" is used.

Justifications were provided for 4826 reports classified as "unclassifiable" by the MAH and 2898 reports classified as "unlikely" by the MAH.

PRAC Rapporteur's comment (for both question 3 d and e)

From a total of 8418 reports

- 14 were assessed as 'possible'

- 4826 as 'unclassifiable'

- 2898 as 'unlikely'

14 cases are assessed as 'possibly related', which is remarkably low. This number is lower than the total number of positive rechallenge cases, in fact 2/3 of the positive rechallenge-cases have been classified as 'unclassifiable' and 'unlikely'. When assessing an ICSR a positive rechallenge is usually considered to strengthen the suspicion of a causal relationship, thus it is highly unusual to classify such cases as unlikely or unclassifiable.

The MAH's justification for their causality assessment when applying 'unlikely' or 'non assessable/unclassifiable' is not endorsed, and a more detailed justification for this is included in the comment to Question 3a. *Positive rechallenge cases have not been detected. The number 43 (cases of positive rechallenge provided by the MAH) is not reflecting the correct number, since several additional positive rechallenge cases have been identified by the PRAC Rapporteur. We have however not reviewed all 7000+ reports, as this was delegated to the MAH hence, we have a "known unknown" of positive rechallenge cases.*

Question 4

In addition to the above-mentioned review which should include all case narratives, the MAH should provide a table as specified below. The table should include all serious and/or positive rechallenge cases and information including the categories shown in the separate columns. The MAH can suggest additional columns, if deemed useful. Data from this table should be easily extractable for assessment. The MAH should prioritize all ICSRs relating to this signal when handling the backlog of cases and report on the backlog at time of DLP.

The MAH should discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for changes to the relevant sections within this discussion.

MAH's response:

The table in excel format (Appendix 2) is containing information for the 8418 requested serious and/or potential rechallenge cases.

There were no backlog cases.

PRAC Rapporteur's Comment:

The MAH did not provide a table as requested. The Excel-file did not include a column for positive rechallenge cases (this was therefore specifically requested in an RSI on 2 Sept.). In addition, the narratives were added in a separate sheet tab and not added to the main listing with ID-numbers included, making it impossible to filter out relevant case narratives. The MAH stated that "Unfortunately, there are limitations in the Excel table cells which prevent import of the entire narrative into the main table listing (in the initial tab in Appendix 1) and there is risk that the large volume of narrative information would be incomplete if added to the data in the main listing." The secondary evaluation therefore required a lot of manual work.

MAH's summary and conclusion:

In summary, no signal for HMB was detected in the large pivotal clinical trial which included women of menstruating age. Indeed, the number of reports of HMB in both the placebo and active vaccine groups, were relatively small when considering the size and length of the study and group differences were not evident. Of the 8418 cases of HMB from the safety database that were the focus of this request, the majority are not medically confirmed and unassessable/unclassifiable or unlikely causally related. While non-medically confirmed reports are taken into consideration, the known inaccuracies in estimations of menstrual blood flow and changes in flow cannot be disregarded, nor can the other limitations of passive reporting for AEs that are not rare. Neither the clinical trial data nor the spontaneously reported data support the EMA PRAC signal assessment report (03 Jun 2022) statement that "…we are under the impression that menstrual disorders are by far the most commonly reported ADRs from women." Finally, the O/E ratios do not indicate that reported events are higher than expected based on background IRs.

Vaccination is, by design, intended to stimulate the immune system and with that stimulation, inflammatory changes, most frequently assessed as systemic reactogenicity events are not unexpected. The potential mechanism by which vaccination with BNT162b2 may trigger HMB is speculative at this time as there is not an understood mechanism that has been elucidated.

Overall, the available data does not support a conclusion that HMB is causally associated with BNT162b2 vaccine. Although no update to the product information or the RMP is planned, this topic will continue to be monitored using routine pharmacovigilance and it is the intention of the MAH to conduct a formal feasibility assessment for evaluation of heavy menstrual bleeding using linked menstrual tracking app data and EMR records in the EU and/or the US.

PRAC Rapporteur's Comment

The MAH emphasizes that the number of reports in the large pivotal clinical trial was low. However, the MAH describes in their response to Q1 the difficulties in investigating HMB in a clinical trial setting (e.g., quantification of menses, quantification of what is a normal menses for the individual participant). Also, reporting in the trial was unsolicited, which further decreases the possibility for AE-reports of HMB, unless patients were hospitalised. Therefore, it cannot be expected that HMB was detected sufficiently in the pivotal studies, and the low reported incidences does not exclude an association. Seen together, the data from the trials are not reassuring (imbalances towards vaccine arms, collection of adverse events not targeting menstrual symptoms/irregularities).

It is the opinion of the PRAC Rapporteur that the limited knowledge regarding the pathophysiological pathway is considered to neither strengthen nor weaken the signal. In this regard the mechanism behind the adverse reaction myocarditis/pericarditis is not understood either but is accepted as an adverse reaction to vaccination with Comirnaty.

The MAH states that there is no support from spontaneously reported data or clinical trial data for the PRAC Rapporteur statement that "…we are under impression that menstrual disorders are by far the most commonly reported ADRs from women". This is disagreed upon. The following table from Vigilyze, searched 15 Sep 2022 shows the top reported PTs for Comirnaty globally, in women aged 18-44. These data support our statement. As can be seen from the table, HMB is the 15th most frequently reported ADR, and menstrual disorder is the 17th most frequently reported ADR. The ADRs reported more frequently than HMB are all described in the SmPC, except for malaise and COVID-19.

Reaction (MedDRA)	Count	Percentage
PT: Headache	111 823	24.1
PT: Fatigue	89 278	19.3
PT: Pyrexia	68 207	14.7
PT: Myalgia	67 928	14.7
PT: Nausea	52 167	11.3
PT: Injection site pain	49 344	10.7
PT: Malaise	48 125	10.4
PT: Chills	47 209	10.2
PT: Lymphadenopathy	37 259	8.0
PT: Dizziness	37 166	8.0
PT: Arthralgia	35 540	7.7
PT: Vaccination site pain	27 082	5.8
PT: Pain in extremity	24 769	5.3
PT: COVID-19	23 086	5.0
PT: Heavy menstrual bleeding	22 288	4.8
PT: Vaccination failure	21 485	4.6
PT: Menstrual disorder	20 022	4.3
PT: Dyspnoea	17 643	3.8
PT: Paraesthesia	17 099	3.7
PT: Pain	14 481	3.1

Regarding causality assessments, it is remarkable that only 0,18% of cases have been assessed as "possible", 37% assessed as "unlikely" and 62% have been assessed as "unclassifiable" by the MAH. The causality assessment provided does not align with the WHO-UMC-guidance document.

The review performed by the MAH has major limitations that precludes an assessment. From a total of 7824 serious cases the MAH discussed ten cases in their response.

The MAH's methodology regarding searching for positive rechallenge cases have identified 43, but several more have been identified after consulting the case narrative. We consider it likely that the total number of positive rechallenge cases exceeds 43, but the exact number is unknown.

Importantly, the nature/characteristics of HMB (lacking a clear definition, subjective and reported from patients) must be taken into consideration when evaluating all available data and the level of support which can be anticipated from Real World Data.

In conclusion, the available data from spontaneous reports and the imbalance in clinical trial data indicate that there is at least a reasonable possibility for an association between vaccination with BNT162b2 and HMB. This is further strengthened by the publication from Trogstad et al including the latest sub-analysis.

4.2. Rapporteur's proposed recommendation

In conclusion, the data submitted in the response has been assessed, and the PRAC Rapporteur remains at our conclusion from the first round of assessment: there is at least a reasonable possibility of a causal association between Comirnaty and heavy menstrual bleeding.

4.3. Comments from other PRAC members and MAH

Comment from MS1:

The proposed recommendation by the signal lead Member State to update the SmPC section 4.8 is not endorsed.

The proposal to update the PI is mainly based on the study by Trogstad et al. including additional confidential analyses provided by NO, few events of heavy menstrual bleeding (HMB) in clinical trials and spontaneously reported cases of HMB.

In the second assessment round, Trogstad and colleagues provided additional analyses to support the findings reported in the published pre-print version. Following the new information, the MS1 still considers that the study is not sufficiently robust to support an update of the PI with HMB. Although 52% of the women used a tracking app, recall bias may have been introduced by the remaining almost half of the study participants. In addition, the potential impact of media attention as well as the fact that the study has not yet been peer-reviewed also warrants cautious interpretation of the study findings.

Regarding case reports, the MAH was requested to provide an updated case review of serious cases and positive re-challenge cases and evaluate the causality of these in the second assessment round.

Overall, the MAH identified 14 cases with 'possible' causal association and 43 cases with positive re-challenge among a total of >8000 case reports. In the assessment report a small subset of these cases were presented of which several contained confounders or lack of important information such as menstruation pattern before vaccination.

It is agreed that the case review provided by the MAH seems non-transparent, and the concerns regarding the causality evaluation and unidentified re-challenge cases posed by the Rapporteur are acknowledged. However, taking into account the challenges in evaluating this common condition, including subjectivity and other factors affecting menstrual bleeding, it is considered that additional relevant information will likely not be obtained by requesting further information from the MAH at this point.

In conclusion, a PI update is not supported. Continued follow-up in the PSUR of this topic is considered appropriate.

PRAC Rapporteur's comment:

We interpret the wording in the SmPC Guideline («...at least a reasonable possibility.»), that the lack of data to establish with *certainty* that there is a causal association should not support the conclusion to *not* update the PI.

Further, we would again like to highlight that our proposal to update the PI is based on the totality of available data, not solely the study by Trogstad et.al. Limitations of this study has been discussed in the report, but we consider that the authors have sought to mitigate these limitations adequately to provide as high a level of evidence as practically attainable for observational studies in the post-marketing setting.

The same principle applies for the statement that additional relevant information will likely not be obtained by requesting further information from the MAH at this point and therefore the issue should be followed up in the PSUR and PI should not be updated. We disagree with this reasoning. We believe that current available data are sufficient to conclude that there is at least a reasonable possibility of a causal association between Comirnaty and HMB.

We consider that PSUR data will not provide additional evidence beyond what has been presented during this signal procedure.

Comment from MS5

We thank the Rapporteur about this preliminary assessment report for the second round and fully agree with the conclusion and proposals for recommendations.
In addition, we fully agree with the Rapporteur about the misinterpretation of some data/criteria by the MAH.
To support the Rapporteur, we would like to add further information as follows:

In MS5, menstrual disorders following vaccination against Covid-19 are closely monitored and analysed since December 27, 2020 in the context of a national safety monitoring for all Covid-19 vaccines. **As of April 2022**, as described in table 1, an initial analysis regarding menstrual disorders identified 3746 cases of haemorrhages with Comirnaty (including 223 serious cases), of which **1457** cases of "Heavy mentrual bleeding" (including 73 serious cases) after vaccination with Comirnaty. Of these 1457 cases, **88 cases (6,0%) showed a positive rechallenge**. To note, 57% of menstrual disorders cases were not resolved at the time of this first analysis. This report regards available data from Decembre 2020 to April 2022.

Table 1: Descriptions of menstrual haemorrhages cases reported cumulatively after vaccination with Comirnaty (up to April 28, 2022)

	Non-serious cases	Serious cases	Total cases
Haemorrhages	3523	223	3746
Intermenstrual haemorrhage	1381	82	1463
Heavy menstrual bleeding	**1384**	**73**	**1457**
Menometrorrhagia	388	37	425
Polymenorrhoea	233	18	251
Vaginal haemorrhage	21	1	22
Postmenopausic haemorrhage	96	11	107
Abnormal uterine bleeding	13	1	14
Uterine haemorrhage	7	0	7

During the previous round in June 2022, in this context and after a qualitative and quantitative analysis of these cases, we supported the update of the SmPC and PL to add a warning regarding this risk (Cominary and Spikevax).

In parallel, we have collaborated for several months with various patients' associations and HCP representatives, including obstetrician-gynecologists specialists, to better quantify and characterise the events related to menstrual disorders following COVID-19 vaccination.

From these reports, as summarised in table 2, an updated analysis regarding cases of menstrual disorders (reported **between 19 July 2022 and 31 August 2022**) has revealed 1665 additional cases of haemorrhages including **837 cases** (428 serious cases) of "heavy menstrual bleeding" with Comirnaty during this period. Of these 837 cases, **50 cases (5.9%) showed a positive rechallenge**[4].

Table 2: Descriptions of menstrual haemorrhages cases reported after vaccination with Comirnaty (reported between July 19, 2022 to August 31, 2022)

	Non Serious cases	Serious cases	Total cases
Haemorrhages	849	816	1665
Intermenstrual haemorrhage	164	99	263
Heavy menstrual bleeding	**409**	**428**	**837**
Menometrorrhagia	107	133	240
Polymenorrhoea	110	106	216
Vaginal haemorrhage	13	5	18
Postmenopausic haemorrhage	15	15	30
Abnormal uterine bleeding	3	1	4
Uterine haemorrhage	28	29	57

These data are still being analysed qualitatively and this is a preliminary analysis.

Although some data were misinterpreted by the MAH (especially the assessment of causality and detection of positive rechallenge), we strongly support the Rapporteur's conclusion that there is at least a reasonable possibility of a causal association between Comirnaty and "heavy menstrual bleeding", considering the following arguments:

- the very high number of reports (>23 000) on heavy menstrual bleeding,

- some of them requiring blood transfusion,
- hundreds of reported cases with positive rechallenge (e.g. more than 100 in MS5).
- two studies (Trogstad and Caspensen) pointing towards an association with heavy menstrual bleeding.

Therefore, the SmPC and PIL should be updated to reflect the current knowledge as proposed by the Rapporteur.

Considering the uncertainties in the mechanism of action, the number of cases with both Spikevax and Comirnaty and heterologous vaccination patterns, such information should also be added in the SmPC and PL of Spikevax.

PRAC Rapporteur's Comment:
We acknowledge the MS supportive comment and thank for for the contribution by efforts at national level in MS5 providing a helpful analysis of MS5 cases. The results presented from MS5 add further data that corroborate the conclusions of the PRAC Rapporteur.

Comment from MS12:

We currently do not see sufficient evidence to include heavy menstrual bleeding in the SmPC as a reaction after the administration of mRNA vaccines. The recording of menstrual characteristics in future studies with different vaccines is encouraged, as this is the only way to make valid statements. Then it can be decided whether heavy menstrual bleeding needs to be integrated into the SmPC and where.

PRAC Rapporteur's Comment:

The PRAC Rapporteur is not of the opinion that the only way to make valid statements is by investigating the issue in future studies. While we agree that further studies should be encouraged to further characterize this issue, we disagree that further studies are necessary to reach a conclusion. This is supported by the SmPC guideline stating that section 4.8 should include adverse reactions "where a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports".

Comment from MS10:

The proposed recommendation by the signal lead Member State to update the SmPC section 4.8 to include "heavy menstrual bleeding" is not endorsed.

In the second round, additional analyses have been presented by Trogstad et al, it should however be noted that the data is still not peer reviewed. Only 52% of the subjects reported any data in the app. As previously mentioned, it is challenging to evaluate a potential causal relationship between a vaccine and heavy menstrual bleeding, a condition that is very common and can be induced by different circumstances/events such as e.g., stress, caloric restriction, or heavy exercise. Furthermore, heavy menstrual bleeding is a subjective, not easily standardized condition. Thus, data from self-reporting or

even questionnaire data are difficult to interpret, especially, as in this case, there has been a lot of attention in the media. As noted in the first round, Trogstad et al reported a generally high incidence of the various menstrual disturbances among menstruating women aged 18–30 years; 37.8% reported at least one change during their last period before vaccination, 39.4% reported at least one change after Dose 1, and 40.9% after Dose 2. A significantly increased risk specifically after the first dose is reported (RR1.90, CI 1.69-2.13). The authors of the study themselves conclude that the interpretation of the study results is limited by several putative confounders such as media attention, a view that can be endorsed. The results from this study only, is not considered sufficient to support an update of the PI.

The additional evidence presented in the first and second round, consisting of data from clinical trials and cases from the MAH global database, does at this stage not provide sufficient support for at least a possible causal association.

Taken together, the available data is not considered sufficient to conclude upon a reasonable causal relationship and SE therefore maintain the position from the first round to not include "heavy menstrual bleeding" in the PI. Nevertheless, the topic should be closely monitored in upcoming PSURs

PRAC Rapporteur's comment:

The MS's position is noted. With regards to the challenges in evaluating this condition, it should be noted that an analysis stratified by reported previous menstrual regularity has been performed and is presented in table 6 (page 63 of this AR). For women who reported that their cycles were always or usually regular, the relative risk of experiencing heavy menstrual bleeding is consistent with the relative risk rates reported for all women. These results demonstrate that the increased relative risk of HMB following vaccination is not driven by reported events in women who usually have irregular menstruation.

With regards to the remaining issues raised by MS10, please see PRAC Rapp's discussion of MS1 comment in which many of the same issues have been raised.

Comment from MS8:

The rapporteur proposal to update section 4.8 of the SmPC is not endorsed.

Overall, we agree that clinical trial setting is not adequate to sufficiently address HMB and that it cannot be expected that HMB was detected sufficiently in the pivotal studies. As a consequence, in principle a low reported incidence does not exclude an association. However, considering that the observed imbalance towards vaccine arm is low and that data collection was not targeted on menstrual symptoms/irregularities, data from clinical trial should be considered not meaningful and not informative for the purpose of this procedure. Moreover, further discussion is warranted about the feasibility of non-interventional studies for addressing this issue.

Whilst acknowledging that the MAH's methodology applied for assessing the cases is questionable and that the number of discarded cases is remarkable, we noticed the lack of well-established case definitions and key information criteria for adjudging the HMB cases. Nevertheless, it should be considered that the overall number of relevant ICSRs is low compared to exposure, accounting for a low reporting rate and a possible reporting bias due to media attention (for us also inferable from the EMA report on EEA cases and media attention). Some relevant information is lacking in part of the re-assessed cases, particularly regarding clinical and pharmacological history. A question that remains open is how to determine the rechallenge and how to perform causality assessment without meaningful

information on menstrual period features before vaccine administration, also taking into account the range and natural variability in menstrual cycles.

Although we agree that some cases of rechallenge have not been considered and adequately assessed in the MAH analysis, we considered the overall number as not relevant, in light of the above-mentioned limitations. In this regard, we remark that the causality assessment undertaken does not align with the WHO-UMC-guidance document and a more accurate and appropriate causality assessment should have been made before drawing any conclusion.

Therefore, we consider that the available data are still not sufficient to support changes in PI at this stage and that further discussion on feasibility of accurate longitudinal studies is warranted in order to address this issue.

PRAC Rapporteur's comment: With regards to the imbalance from clinical trials, we acknowledge that the numbers are small and cannot be considered as conclusive evidence. However, in a trial of this size, risk factors are assumed to be evenly distributed. Therefore, a numerical imbalance should not be ignored. A numerical imbalance was not ignored for facial paralysis and this ADR was included in section 4.8 of the SmPC.

We agree with the MS that a further discussion about the feasibility of non-interventional studies is warranted. The MAH's proposal in this regard has been accepted by the PRAC Rapporteur. The MAH has requested an additional two months to perform a feasibility assessment regarding non-interventional studies.

The MS comments that the overall number of relevant ICSRs is low compared to exposure, accounting for a low reporting rate and a possible reporting bias due to media attention. We do not agree on this. While we acknowledge the inherent weakness of ICSRs with regards to lack of complete clinical history, we do not agree that this is an issue specifically related to this signal. We consider that a large number of reports include sufficient information to be considered relevant for the assessment of this signal. As detailed in the Assessment Report, we do not agree with the MAH's case review and their selection of relevant cases. In addition to the case review, we consider that the number of ICSRs for HMB relative to other reported PTs is strengthening the signal. Globally, the number of ICSRs regarding menstrual disorders is ranked high compared to other PTs reported for the same vaccine, e.g there are 111 000 reports of headache and 22 000 reports of heavy menstrual bleeding, i.e. the general level of reporting for this particular product should be taking into consideration when commenting on the actual number of reports. Reporting rates are known to vary according to several factors. One of them being the severity of the reaction. A prolonged menstrual period and/or a heavy menstrual bleeding is not necessarily experienced as dramatic and/or severe, especially if it is self-limiting – and this factor is known to influence the likelihood for a reaction to be reported. Also, time to onset from vaccination until the reaction appears, is a factor thought to influence the reporting rate. For this particular signal there is a TTO up to several weeks, thereby reducing the chance of reporting. Taking into consideration that there is a known underreporting in general for adverse reactions, and the factors mentioned which further reduces the likelihood for reporting, we do not share the opinion that the reporting rate is low, and that media coverage is weakening the signal.

Regarding the number of positive rechallenge cases, we agree that the exact number of cases is of less relevance. The fact that there exist several cases of positive rechallenge is, however, an important factor to have in mind when assessing causality.

Comment from MS11:

The PRAC Rapporteur's thorough and critical assessment is highly appreciated.

However we conclude that the data assessed in the current round do not provide important new insights to strengthen the current signal.

This also applies to the latest supplemental sub-analysis by Trogstad et al. (see more detailed comments below).

Consequently, the current evidence is insufficient to support an update of the product information.

Regarding supplemental sub-analysis by Trogstad et al.

Although the authors observed a relative risk of experiencing heavy menstrual bleeding (HMB) following COVID-19 vaccination of 2.00 (CI: 1.54-2.60) after dose 1 and 1.64 (1.33-2.01) after dose 2, robustness of this finding is questioned. Based on the currently provided information it cannot be agreed that the at least a reasonable possibility for an association between vaccination with BNT162b2 and HMB is further strengthened by the publication from Trogstad et al including the latest sub-analysis.

Several issues around the conduct of the study have not been clarified and therefore this study does not allow to conclude on an increased risk of HMB with Comirnaty exposure:

1. It is unclear whether the supplemental tables are based exclusively on women using the tracking app or whether cycle history is obtained from a mix of app and questionnaires. Therefore, completeness of data and possibility of recall bias cannot be estimated.

2. Tables provide only information regarding last cycle prior to dose 1 (or 2), which is too limited to establish cycle regularity. In order to assess pre-vaccination variety at base line, more cycles prior to receiving vaccination should have been available.

3. It is understood that the number and prevalence of menstrual disturbances before and after vaccination in Supplemental tables 2 and 3 have not been adjusted for confounders and no sensitivity analyses have been performed, e.g. by excluding history of infections (incl SARS-CoV-2), concomitant medication, presence of alternative etiologies, risk factors, ultrasound abnormalities, BMI.

@1. The PRAC Rap states that 'The number of women who report using a menstruation tracking 'app' was approximately 52 %. As discussed previously, this aid the responders in completing the questionnaires, thereby reducing recall bias.' This is understood as that in half of the women cycle history was not tracked and based on questionnaires (i.e. women's recollection) only. Consequently, some reduction of recall bias only applies to half of the women, because no prospective pre-vaccination cycle tracking data are available from the other half (i.e. women not using the tracking app).

Moreover it is unclear how representative the women using the menstruation tracking app are for the entire population. As seen in the US studies these are generally younger and higher educated (owning a smart phone). A reason why women are inclined to use the app might be to keep track of their usually unpredictable cycle in the first place.

Regarding MAH's discussion for further investigating HMB (Q1)

The MAH's initiatives to further investigate this issue e.g. by collecting additional information from clinical trial participants reporting AEs of HMB are welcomed.

The PRAC Rapporteur's concern that 'there is a risk that events of heavy menstrual bleeding are insufficiently detected, potentially leading to underestimation.' is not supported. In the post-marketing setting women have reported HMB in large numbers, and we do not see a reason why they would be less inclined to do so within the context of a clinical trial.

Regarding the additional data collection form that is mentioned, the PRAC Rapporteur asked the MAH to consider including questions whether menstrual flow was increased following vaccination with the primary series. This way of phrasing the question is not supported. A more neutral/objective (i.e. less suggestive) line of questioning should be proposed, e.g. 'Was the menstrual flow same as normal/less than normal/more than normal?'

Evidently, proposals for additional studies should take into account strengths and weaknesses of previous studies, i.e. adequate study design to minimise bias or confounding.

Regarding the question whether conducting non-interventional studies is feasible, the timeline for completion of this feasibility assessment is expected within 2 months.

Regarding evaluation of clinical trial data (Q2)

When adjusted for exposure in females of childbearing age a slight trend towards an imbalance of HMB to the detriment of the vaccinated group is observed, but this can hardly be considered an imbalance, as the 95%CIs are overlapping due the very few identified cases (i.e. 1 vs. 0 and 3 vs. 2, in tables 13 and 14, respectively). Moreover it is noted that this trend apparently is not specific for Heavy Menstrual Bleeding, rather also for any adverse event.

After unblinding, the earliest event start date was 7 days post vaccination and the latest was 115 days post vaccination (mean days post vaccination = 35.5), with an event duration of 6-143 days (mean duration = 39.6 days, 1 event end date was unknown). This represents a very broad range in TTO, and it is assumed that cases with a very long TTOs are considered unlikely supportive for causality, due to (non-vaccination-related) intermittent events (including normal menses).

Regarding updated case review (Q3)

The PRAC Rapporteur's critical comments regarding the MAH's overly restrictive /conservative triage and interpretation of WHO causality scaling, and inadequate response to PRAC requests are endorsed. It is agreed that instead of MAH's causality assignment unlikely, in some cases causality may be upgraded to possible at most (in absence of other etiologies), but there are still no cases with probable causality.

The PRAC Rapporteur's comment regarding positive rechallenge cases is endorsed. However, while it is important to know the number of positive rechallenge cases (hence supportive for causality), it is equally important to have information on number of cases reporting a negative rechallenge (unsupportive), since with the high background rate of HMB a chance finding is well possible and the proportion of potentially supportive cases should be put into context.

As general comment for future assessments, in order to allow meaningful secondary assessment the MAH is expected improve their methodology in order to apply a less conservative approach for dismissing cases as non-supportive for causality. For the current signal based on the thorough case review of the PRAC Rapporteur it is concluded that assessment of causality of HMB based on

spontaneous reports remains challenging considering the high background, high variation, subjective nature of the AEs.

In summary, it is agreed that the case review performed by the both the MAH and PRAC Rapporteur has limitations, and remains inconclusive regarding the causal relation between vaccination and HMB. Consequently, it also means that as in the previous round the current evidence is insufficient to support an update of the product information.

Regarding pathophysiological mechanism (Q4)

The limited knowledge regarding the pathophysiological pathway is considered to neither strengthen nor weaken the signal. Consequently, the current evidence is inconclusive and unaltered relative to the adopted PRAC conclusion from the previous assessment round.

Comparing the signal of HMB to myocarditis is not considered a valid argument to support labelling as ADR in SmPC section 4.8, amongst others because:

- For myocarditis a consistently [in different geographical locations, e.g. US, EU, Israel, and in independently conducted observational studies] increased risk was observed in particular age groups, risk windows/TTO, above the background incidence.
- Case identification relies on medical confirmation [which is more objective than for HMB]
- Myocarditis is a potentially serious adverse reaction, warranting early detection, diagnosis, to allow adequate management

These points do not apply to HMB.

It is agreed that an established plausible mechanism is not a prerequisite for labelling (it never is), but all available evidence should be taken into account and should be supportive in its entirety.

It is reiterated that in isolation and in absence of exclusion of other etiologies a high number of observed Adverse Events (not ADRs as the PRAC Rap states) is neither unexpected, nor sufficient to support causality. Especially considering the high background, high variation, subjective nature of the AEs.

PRAC Rapporteur's comment:

The detailed and comprehensive comment by the MS is appreciated.

Regarding the Trogstad study: The MS comments that "Several issues around the conduct of the study have not been clarified…" Please find clarifications on the issues detailed below.

1. The study was based on a questionnaire, and 52% of the respondents said that their response in the questionnaire was aided by the use of an app.

2. Cycle regularity is not based on the last period prior to vaccination. To account for previous cycle variability, an analysis stratified by reported previous menstrual regularity has been performed, which we would like to remind the MS of (table 6, page 63 of this AR). For women who reported that their cycles were always or usually regular, the relative risk of experiencing heavy menstrual bleeding following COVID-19 vaccination was consistent with the relative risk rates reported for all women. These results demonstrate that the increased relative risk of HMB following vaccination is not driven by reported events in women who usually have irregular menstruation.

3. The MS states that it is understood that the number and prevalence of menstrual disturbances before and after vaccination in Supplemental tables 2 and 3 have not been adjusted for confounders and no sensitivity analyses have been performed. This is not correct - these factors have been adjusted for, and the data was provided in the AR in the first assessment round.

Trogstad et al has performed several sensitivity analysis:

- Disease in the uterus/cervix (myoma, endometriosis, PCOS, HPV infection, abnormal cervical cells, ovarian cyst, «other diseases») - page 20.

- Positive SARS COV-2: women with positive test for SARS-COV-2 within 6 weeks after dose 1 or dose 2 have been excluded as a sensitivity analysis – page 21

- Use of contraception – page 22

The factor that remains on the MS's list of factors that should be included in a sensitivity analysis is BMI. The other factors have been analysed.

The MS states that users of a menstrual app might have irregular cycles – we consider this statement to be speculative. Q1: Regarding MAH's discussion for further investigating HMB

The comment that it cannot be concluded that the settings in clinical studies are different from the post-marketing setting regarding incentive to spontaneously report an adverse event is endorsed.

We endorse the suggestion to phrase the question in the additional data form to the lines of 'Was the menstrual flow same as normal/less than normal/more than normal?' We would like to point out that an exact wording of this question was not imposed on the MAH, but a suggestion for consideration.

Further details regarding the MAH's proposal on how the issue can be addressed in studies are expected later, as the MAH proposes to submit a feasibility assessment within two months, which has been accepted. Therefore, additional specifications regarding this study design have not been requested in this assessment round.

Q2: Regarding evaluation of clinical trial data

Regarding TTO – following vaccination there is a window of approximately six weeks where immunological responses might occur. We are therefore in disagreement with the MS statement that "very long TTOs" (not otherwise specified) are considered unlikely supportive of causality. Another important consideration is that menstruation can occur several weeks after vaccination depending on what day of the cycle vaccination took place, therefore a long TTO is not unrealistic seen from a medical point of view.

Regarding the MS comment on statistical significant imbalances – we have never stated that there is a statistical significant difference but has commented on the numerical imbalance. Statistical significant differences are not expected to be identified, since the study was not powered to detect this.

Q3: Regarding updated case review

Cases of negative rechallenge were not part of the LoQ initially and have therefore not been assessed specifically. Additionally, as there is no field in the ICSR form for "negative rechallenge" as opposed to "positive rechallenge", cases of "negative rechallenge" are not easily retrievable from e.g. EudraVigilance. As the potential effect of the vaccine on the female reproductive system (an on average 28 days cyclic system) remains unknown, and a TTO is not defined, we would be hesitant to emphasize the lack of negative rechallenge cases, although we understand and acknowledge the theoretic reasoning behind the principle.

It is agreed that the case review presented by the MAH has limitations. However, based on qualitative assessment of countless case narratives, and the fact that there are cases of positive rechallenge, as well as other data that has been included in the report, we remain at our conclusion from the first round. This has been thoroughly justified elsewhere in the report. We respect that the MS was of another opinion in the first round, and since the case review was of a limited value the MS maintains their position – as do we.

Q4: Regarding pathophysiological mechanism

The purpose behind our comment regarding the lack of pathophysiologic mechanism was to address one of the main arguments presented by the MAH, and we wanted to stress that the *lack of* a mechanistic explanation is not valid as an argument to *dismiss* a potential link, mentioning myocarditis as an example. We did not intend to compare the data and level of evidence between the two reactions, and it was not intended as an argument to include this in section 4.8. We agree with the MS that this is not a valid argument.

We do however disagree with the statement regarding several factors not being relevant for HMB as pointed out by the MS. The importance of early detection does also apply to a heavy menstrual bleeding, since a persisting menstrual bleeding could prevent women from conceiving and, secondarily, family planning. Further, a heavy menstrual bleeding which impacts daily living, in some instances requiring hospitalisation, treatment with iron or blood transfusion and lasting for months, is also a serious condition.

Comment from MS2:

First, we would like to thank Norwegian colleagues for the very careful assessment. The data from the Trogstad study confirms at least possible causal relationship between vaccination with Comirnaty and heavy menstrual bleeding. The study is further supported by the Caspersen et al. study in adolescent girls and the little imbalance in the clinical studies. The MAH proposed to perform a PASS where the data from the menstrual apps and EMR are planned to be assessed. We support the PASS, but we don´t understand why only the apps without EMR are planned in EU in view that the MAH plans to validate the data from the apps with the data from EMR. Therefore, the MAH should explain the plan for validation of the data from EU. The second question is about the expected high percentage of women which probably will not attend the physicians and therefore their data will not be validated in EMR. How will be these cases assessed?

The result of the MAH´s assessment cannot be supported. It is not usual that only 14 from 7824 reported cases are assessed as possibly related and concurrently the number of the possible cases is markedly lower than the number of cases with rechallenge. Additionally, the MAH used the methodology not allowing to detect all the cases with rechallenge. The MAH´s over-conservative approach of the causality assessment and the incorrect search of the cases with rechallenge do not allow the meaningful assessment of the provided data. As was highlighted in AR, it is not possible to exactly quantify heavy menstrual bleeding. We think that we can´t also expect that higher percentage of the cases confirmed by the physicians in future and the problems with the causality assessment of the patient reports can be therefore further anticipated. As the assessment of this issue will probably persist based on the patient reports the role of the patient reports in the assessment should be better specified. The fact that PT heavy menstrual bleeding is the 17th most frequently reported PT in Vigilyze should not be also ignored.

Based on the data from Trogstad study, Caspersen study and based on the little imbalance in the clinical trials we find the causal association between heavy ME bleeding and Comirnaty at least possible and therefore, we support the Rapp´s conclusion to add the ADR Heavy menstrual bleeding to the PI.

PRAC Rapporteur's comment:

The comment and endorsement of our conclusion to update the PI are highly appreciated.

Regarding the non-interventional studies proposed by the MAH, we share the same concerns as the member state, as we have concluded in our assessment of Q1 in section 4.1.2. We appreciate this support. The MAH has not submitted a final proposal for the non-interventional studies, which awaits a feasibility report. Further details are expected for review later.

Comment from MS6:

We fully endorse the Rapporteur's conclusion and have no further comments.

PRAC Rapporteur's comment:

The endorsement is highly appreciated.

Comment from MS3:

We overall agree with PRAC Rapporteur to include heavy menstrual bleeding in section 4.8 of the product information due to the following reasons:

-Although the number of cases in clinical trials is very small, a numerical imbalance and a higher incidence rate of heavy menstrual bleeding in subjects receiving study drug than placebo is identified.

-The different sensitivity analyses by Trogstad et al showed consistent results, even when only women with previous normal menstruation are analysed. The study by Carpensen et al in adolescent also showed the same pattern of results, although the same sub analyses are not presented.

-In addition, there are other studies with different designs that showed similar results. A cross-sectional study published by Baena et al showed that of 14,153 women who had received the full course of vaccination at least three months earlier, 11,017(78% of them) reported menstrual changes. The most predominant menstrual changes was heavy menstrual bleeding –HMB- (43%). To note that although this study is a self-reported study, the survey was conducted shortly after the end of the vaccination campaign to avoid recall bias. In addition, in a systematic review of 14 studies including 78 138 females vaccinated, 52,05% (39 759 women) showed menstrual disorders. Menorrhagia, metrorrhagia and polymenorrea were the most commonly reported problems (Nazir M et al, 2022).

-Regarding the spontaneous cases, we concur with the Rapporteur that the number of cases with positive rechallenge would be higher than the reported by the MAH. In addition, the number of serious cases of HMB has increased from previous AR.

-According to the Rapporteur, in Vigilyze heavy menstrual bleeding (HMB) is the 15th most frequently reported ADR and the other ADRs more frequently than HMB are already listed in the SmPC. In the MS3 database with data until 22 May 2022, HMB is the 16th most frequently reported with Comirnaty and the other ADRs more frequently than HMB are also already listed.

Therefore, we consider that available data support the inclusion of information in the SmPC (section 4.8), so that women are informed. Information about the nature (transient and mild) of these ADRs should also be included as a footnote.

References:

Baena-García L, Aparicio VA, Molina-López A, Aranda P, Cámara-Roca L, Ocón-Hernández O. Premenstrual and menstrual changes reported after COVID-19 vaccination: The EVA project. Womens Health (Lond). 2022 Jan-Dec;18:17455057221112237. doi: 10.1177/17455057221112237. PMID: 35833668; PMCID: PMC9289916.

Nazir M, Asghar S, Rathore MA, Shahzad A, Shahid A, Khan AA, Malik A, Fakhar T, Kausar H, Malik J. Menstrual abnormalities after COVID-19 vaccines: A systematic review. Vacunas. 2022 Jul 19;23:S77–87. doi: 10.1016/j.vacun.2022.07.001. Epub ahead of print. PMID: 35873308; PMCID: PMC9294036.

PRAC Rapporteur's comment:

The endorsement and detailed justification are highly appreciated.

The data presented from MS3 corroborate the data assessed in the report and the conclusion of the PRAC Rapporteur.

Regarding the proposed footnote and the wording of "transient and mild in nature": as was commented on during the first round of assessment: the current evaluation did not investigate the characteristics of the heavy menstrual bleeding such as its duration, and therefore we would be cautious to include information on severity and duration in the Product Information at this stage.

Comment from MS4:

Although evidence to demonstrate an association between Comirnaty and heavy menstrual bleeding is not very strong, such association cannot be completely excluded. After considering epidemiological data, some well-described cases and the cases with positive rechallenge, MS4 considers that a causal association is reasonably possible and supports the inclusion of "heavy menstrual bleeding" in 4.8.

MS4 suggests that the focus of future studies is enlarged to include also other menstrual disorders.

PRAC Rapporteur's comment:

The endorsement is appreciated.

4.4. Updated rapporteur's proposed recommendation

Based on currently available evidence the PRAC Rapporteur considers that the SmPC/PIL should be updated with information regarding heavy menstrual bleeding. The MAH is asked to propose a frequency category.

The wording in of the proposed update to section 4.8 of the SmPC has been amended in accordance with the MS comments.

Text for SmPC

Section 4.8: Heavy menstrual bleeding.

Text for PIL

Section 4 (possible side effects): Heavy menstrual bleeding

4.5. Adopted PRAC recommendation

Having considered all the available evidence, including spontaneous case reports in EudraVigilance, data from national reviews, observational studies, and provided by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH for COVID-19 mRNA vaccine (nucleoside-modified) Comirnaty (BioNTech Manufacturing GmbH) should submit by 25 November 2022 a variation to amend the product information as described below (new text underlined):

Summary of Product Characteristics

Section 4.8 Undesirable effects

System Organ Class: Reproductive system and breast disorders

[Frequency] Not known: Heavy menstrual bleeding*

[Under table] * Most cases appeared to be non-serious and temporary in nature.

Package leaflet:

Section 4 - Possible side effects

Not known (cannot be estimated from the available data):

Heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)