NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA efficacy supplement
Application Number(s)	021225/S42
Priority or Standard	Standard
Submit Date(s)	October 13, 2020
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PDUFA Goal Date	August 13, 2021
Division/Office	Division of Urology, Obstetrics, and Gynecology (DUOG) Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Review Completion Date	August 10, 2021
Established/Proper Name	levonorgestrel-releasing intrauterine system
Trade Name	Mirena
Pharmacologic Class	progestin-containing intrauterine system
Applicant	Bayer HealthCare Pharmaceuticals Inc
Dosage form	Contains 52 mg of levonorgestrel, inserted into the uterus
Applicant proposed Dosing Regimen	Insertion every 7 years
Applicant Proposed Indication(s)/Population(s)	Intrauterine contraception for up to 7 years
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Intrauterine contraception for up to 7 years
Recommended Dosing Regimen	Insertion every 7 years

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OPDP, Office of Prescription Drug Promotion
OSE, Office of Surveillance and Epidemiology
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BMI	body mass index
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COA	clinical outcome assessment
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DCEP	Division of Cardiometabolic and Endocrine Pharmacology
DEPI	Division of Epidemiology
DMEPA	Division of Medication Error Prevention and Analysis
DUOG	Division of Urology, Obstetrics, and Gynecology
ECG	electrocardiogram
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice
HMB	heavy menstrual bleeding
HCP	healthcare provider
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IUS	intrauterine system
LARC	long-acting reversible contraception
LNG	levonorgestrel
MBL	menstrual blood loss
MedDRA	Medical Dictionary for Regulatory Activities
MET	Mirena Extension Trial

mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
OCP	Office of Clinical Pharmacology
OPQ	Office of Pharmaceutical Quality
ORPURM	Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PHE	public health emergency
PI	Pearl Index
PID	pelvic inflammatory disease
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSP	pediatric study plan
PT	preferred term
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SHBG	sex hormone binding globulin
SOC	system-organ class
T-body	T-shaped polyethylene frame
TEAE	treatment emergent adverse event
TVUS	transvaginal ultrasound
UPT	urine pregnancy test
US	United States
USPI	US Prescribing Information
WY	woman-years

1. Executive Summary

1.1. Product Introduction

Bayer HealthCare Pharmaceuticals Inc. (hereafter referred to as the Applicant) is seeking approval to extend Mirena duration of use up to 7 years for the indication of contraception. Mirena is a levonorgestrel (LNG)-containing intrauterine system (IUS) approved on December 6, 2000, by the U.S. Food and Drug Administration (FDA) for up to 5 years of continuous contraception. On October 1, 2009, the Agency approved Mirena for the treatment of heavy menstrual bleeding (HMB) in women who choose to use an IUS as their method of contraception. The most recent efficacy supplement approval of Mirena, issued on August 20, 2020, was reviewed under S-040, which increased the duration of Mirena use for contraception up to 6 years.

Mirena IUS consists of a T-shaped polyethylene frame (T-body) with a drug product (LNG) on the stem and is packaged with an inserter (Bayer HealthCare Pharmaceuticals 2021a). The IUS is regulated as a drug with the inserter considered a device. Together, they form a single entity drug-device combination product with an initial release rate of approximately 20 mcg/day of LNG. The T-body, made of polyethylene, contains a steroid reservoir (hormone-elastomer core) around the vertical stem. The reservoir consists of a mixture of 52 mg of LNG and polydimethylsiloxane. The reservoir is covered with a polydimethylsiloxane membrane (b) (6) The polyethylene of the T-body is compounded with barium sulfate, which makes it radiopaque. The T-body has a loop at one end with polyethylene threads attached for removal.

Mirena is one of four LNG IUSs approved in the United States for contraception. Liletta IUS also contains 52 mg of LNG and is approved for up to 6 years of use. Kyleena and Skyla IUSs contain 19.5 mg and 13.5 mg of LNG and are approved for up to 5 years and 3 years of use, respectively. The Applicant is the new drug application (NDA) holder for Mirena, Kyleena, and Skyla. Mirena is the only IUS with the additional indication for treatment of HMB. The mechanism of action for LNG IUSs has not been conclusively demonstrated. Possible mechanisms of action that assist in prevention of pregnancy include thickening of cervical mucus preventing passage of sperm into the uterus, inhibition of sperm capacitation or survival, and alteration of the endometrium.

1.2. Conclusions on the Substantial Evidence of Effectiveness

In this submission the Applicant has demonstrated that use of the intrauterine system Mirena (NDA 021225) maintained substantial evidence of contraceptive effectiveness during Year 7 of use. Evidence generated from study 18649, also known as the Mirena Extension Trial, confirmed that the primary efficacy endpoint (Pearl Index, or PI) remained at an acceptable level for an intrauterine system in this additional year of product use.

The general formula for the PI is as follows:

$$\text{Pearl Index} = \frac{\text{number of on-treatment pregnancies}}{\text{evaluable exposure time (i.e., number of woman-years)}} \times 100$$

On-treatment pregnancy was defined as a pregnancy with a date of conception that occurred during the sixth and seventh year of treatment within 7 days after the end of exposure as well as a pregnancy that occurs after partial expulsion or first occurrence of non-compliance but before Mirena removal.

Evaluable exposure time was defined for the primary analysis as the number of complete and incomplete 28-day cycles in which no backup contraception was used (based on eDiary data).

The Pearl Indices for Year 6 and 7 combined and individually are shown in Table 1 below:

Table 1. Pearl Index: Primary Analysis Based on Complete/Incomplete 28-Day Cycles (PAS Year 7)

Year	N	Number of Pregnancies	Evaluable Time of Exposure [cycles/wy]	Pearl Index (95% CI)
2-year (Years 6 and 7)	353	2	6645.2/509.77	0.39 (0.05, 1.42)
Year 6	353	1	3732.8/286.35	0.35 (0.01, 1.95)
Year 7	291	1	2912.4/223.42	0.45 (0.01, 2.49)

Source: Reviewer's Analysis and Clinical Study Report of Study 18649 year 7: Table 14.2.1/2

The Pearl Indices and the 95% confidence intervals in the preceding table are consistent with pregnancy rates historically seen with intrauterine systems. There has been no evidence of any significant diminution of contraceptive efficacy in Year 7 of Mirena use.

One clinical review issue was whether body mass index decreases the effectiveness of an LNG contraceptive, although for an IUS the primary effect is local. One pregnancy occurred in Year 7 of Mirena use in a women with a BMI <30 kg/m^2. Although the numbers are small and preclude a full analysis, the local contraceptive effects of intrauterine systems may play an important role in maintaining effectiveness in a population with a higher BMI. The percentage of women in Study 18649 with a BMI ≥30 kg/m^2 was approximately 31%.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In this NDA efficacy supplement (NDA 021225 S-42) the Applicant provided clinical and clinical pharmacologic data to support contraceptive use of Mirena in Year 6. The clinical efficacy and safety data were obtained from the Mirena Extension Trial (MET) which enrolled women who were in their 5th year of Mirena use. Although the Applicant initially attempted to enroll women who had Mirena placed to treat heavy menstrual bleeding (HMB), they were unable to enroll sufficient numbers to establish their HMB indication past the previously approved 5 years of use.

As noted in Section 1.2, the Applicant's PI results demonstrated substantial contraceptive effectiveness for Mirena in Year 7 with only one on-treatment pregnancy reported.

The safety of Mirena in Year 7 was also demonstrated. There have been no deaths reported in Year 7 of study 18649. There were 5 subjects who had serious adverse events (SAEs) reported in Year 7. These cases included one suicidal ideation (preceded by suicide attempt in a study subject with a past history of depression and history of discontinuing her medications), one ectopic pregnancy (medically treated), one partial uterine perforation, one embedded device, and one participant with worsening obesity (treated by gastric bypass). The subjects with suicidal ideation and obesity were continued on their Mirena contraceptive. The other three had removal of the system.

Most of the other discontinuations due to adverse events in Year 7 were related to bleeding, breast swelling and tenderness, pelvic pain and device expulsion. There were no increased rates of adverse events of special interest in Year 7 (perforation, pelvic infection, ovarian cysts and ectopic pregnancy). Treatment emergent adverse events in Year 7 were generally similar to those encountered in Year 6 with some increase reporting of weight gain and anxiety reaction. Safety analysis found a slight increase in weight gain (7.7% gaining 10 kg or more). Uterine bleeding patterns and amenorrhea were consistent with previous Mirena years of use and represented no new safety concerns for an LNG IUS. Overall in Study 18649, there were no new safety signals in Year 7 or significant increases in safety reporting frequencies.

The Applicant's "Summary of Postmarketing Reports on patients who used a single Mirena for greater than 5 years" indicated the following:

- No increased frequencies of individual AEs by duration of use up to eight years of Mirena use
- Complication of device removal was the most common AE reported
- Device breakage occurs with complication of device removal (e.g., embedment)

There were no approvability issues reported by the disciplines reviewing this supplement (chemistry, nonclinical pharmacology/toxicology, clinical pharmacology, biostatisics and clinical). CDRH, which regulates use of the inserter, identified no concerns with that device. In addition,

although some changes to patient monitoring were made due to the public health emergency (coronavirus pandemic), these changes were determined to be unlikely to alter the effectiveness or safety results from this trial. Overall, the benefit-risk profile for Mirena to extend the contraceptive indication through Year 7 is favorable and supports approval.		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition	• Unintended pregnancy has significant personal, societal, and health consequences for women and their families.	Extending the use of long-acting contraceptives contributes to the overall goal of preventing unintended pregnancy.
Current Treatment Options	• Long-acting reversible contraceptive (LARC) methods include intrauterine systems and implants. • LARCs are effective for 3 to 10 years depending on the product. They are less dependent on user compliance and have been shown to be highly effective contraceptives over extended periods of time. • Of the intrauterine systems marketed in the United States, four are LNG-releasing and one releases copper. There is one LARC dermal implant currently marketed.	In the last 20 years LARCs have become the contraceptives of choice for many women in the US who seek highly effective methods that are less user-dependent
Benefit	• In study 18649 there was only one pregnancy in 2,912 evaluable cycles. • The Pearl Index (PI), based on the Applicant's data for complete and uncomplete cycles analysis year 7, was 0.45 (95% CI: 0.01, 2.49).	Contraceptive effectiveness was demonstrated by acceptable PI results.
Risk and Risk Management	• There have been no deaths reported in Study 18649 • Serious adverse events in Year 7 include suicidal ideation (1), ectopic pregnancy (1), embedment (1), partial perforation (1) and worsening obesity with gastric bypass surgery (1) • Safety results from Year 7 use are similar to Year 6	There were no new safety findings or any significant increases in percentages of any known safety signal during Year 7 of Mirena use. Presciption labeling was revised to update the postmarketing safety profile

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Postmarketing reports from patients keeping Mirena in place longer than 5 years have not revealed any increased safety findings with duration of use extending to eight years.	

1.4. Patient Experience Data

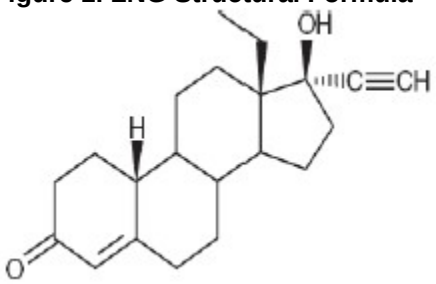
Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			**Section of review where discussed, if applicable**
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Bleeding Diary Section 8.2.5.1
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

Mirena contains 52 mg of LNG, a progestin, and is intended to provide an initial release rate of approximately 20 mcg/day of LNG. Levonorgestrel USP, (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one, the active ingredient in Mirena, has a molecular weight of 312.4, a molecular formula of $C_{21}H_{28}O_2$, and the following structural formula (Figure 1):

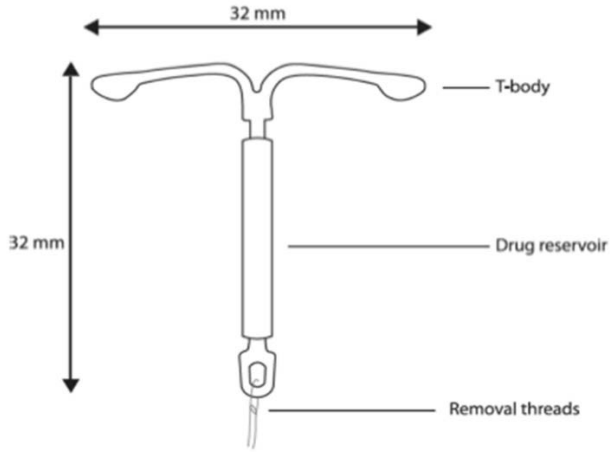
Figure 1. LNG Structural Formula



Source: Mirena approved label
Abbreviations: LNG, levonorgestrel

Mirena consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir (hormone elastomer core) around the vertical stem (Figure 2). The white T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. The reservoir consists of a cylinder, made of a mixture of LNG and silicone (polydimethylsiloxane. The reservoir is covered by a semi-opaque silicone membrane, composed of polydimethylsiloxane and colloidal silica. The T-body is 32 mm in both the horizontal and vertical directions. The polyethylene of the T-body is compounded with barium sulfate, which makes it radiopaque. A monofilament brown polyethylene removal thread is attached to a loop at the end of the vertical stem of the T-body. The polyethylene of the removal thread contains iron oxide as a colorant. The components of Mirena, including its packaging, are not manufactured using natural rubber latex.

Figure 2. Mirena IUS

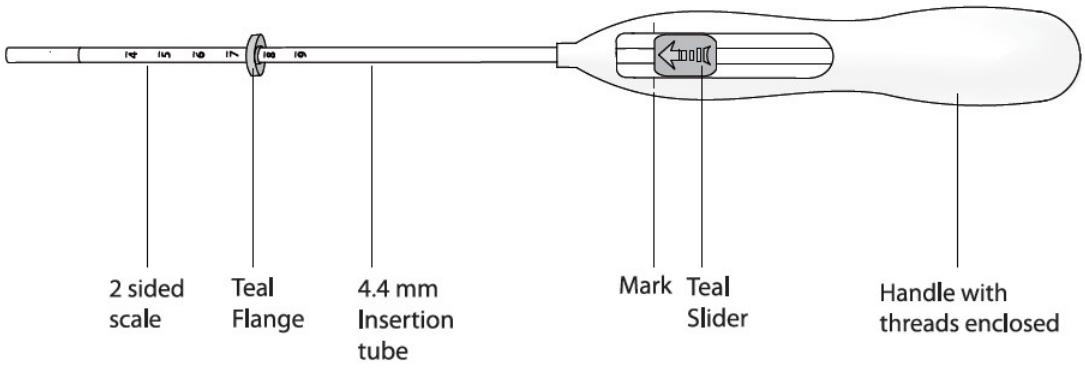


Source: Mirena approved label.
Abbreviations: IUS, intrauterine system; T-body, T-shaped polyethylene frame

Mirena is packaged sterile within an inserter. The inserter (Figure 3), which is used for insertion of Mirena into the uterine cavity, consists of a symmetric two-sided body and slider that are

integrated with flange, lock, pre-bent insertion tube and plunger. The outer diameter of the insertion tube is 4.4 mm. The vertical stem of Mirena is loaded in the insertion tube at the tip of the inserter. The arms are pre-aligned in the horizontal position. The removal threads are contained within the insertion tube and handle. Once Mirena has been placed, the inserter is discarded.

Figure 3. Mirena Inserter



Source: Mirena approved label.

Mirena is inserted into the uterine cavity by a healthcare provider under aseptic techniques.

2.1. Analysis of Condition

Reproductive and sexual health care, including the provision of contraceptive services, is a key intervention by which the health of women can be improved and is recognized as a human right (World Health Organization 2020). In 2011, there were 45 unintended pregnancies for every 1,000 women aged 15-44 in the United States (US). Nearly half (45%, or 2.8 million) of the 6.1 million pregnancies in the US were unintended. Of these unintended pregnancies, 42% ended in abortion (Guttmacher Institute 2019). Induced abortion may have psychological/emotional consequences and raise moral or ethical issues (Brown and Eisenberg 1995). Unintended pregnancy leading to the birth of a child may have a negative impact on neonatal outcomes and maternal and infant health (Hatcher et al. 2018).

2.2. Analysis of Current Treatment Options

Contraceptive methods are broadly divided into irreversible and reversible. Reversible contraceptives can be divided into long-acting or short-acting. Short-acting methods require daily, weekly, or monthly administration (e.g., oral contraceptives, rings, patches). Long-acting reversible contraceptive (LARC) methods are approved as effective for 3 to 10 years depending on the product. LARCs, including Mirena, are less dependent on user compliance and have been shown to be highly effective contraceptives over extended periods of time. Recently, the American College of Obstetrics and Gynecology recommended LARCs be routinely offered to most women (Committee on Practice Bulletins-Gynecology and Long-Acting Reversible Contraception Work Group 2017).

FDA-approved and marketed LARCs include five IUSs and one implant. The implant and four of the IUSs contain a progestin, while one IUS (ParaGard) contains copper. The products with their characteristics are listed in Table 2 below:

Table 2. Currently Available Long-Acting Reversible Contraceptive (LARC) Methods

Product Name Approval Date NDA Number	Formulation Site	Duration of Use (Years)	Device Size Length x Width	Progestin Release Rate
Mirena 2000 NDA 021225	52 mg LNG IUS	6	32 mm x 32 mm	Initial – 20 mcg/day 1 year – 18 mcg/day 5 years – 10 mcg/day 6 years - 9 mcg/day 7 years – 8 mcg/day
Liletta 2015 NDA 206229	52 mg LNG IUS	6	32 mm x 32 mm	Initial – 20 mcg/day 1 year – 17.5 mcg/day 5 years – 9.9 mcg/day 6 years – 8.6 mcg/day
Kyleena 2016 NDA 208224	19.5 mg LNG IUS	5	30 mm x 28 mm	Initial – 17.5 mcg/day 1 year – 9.8 mcg/day 5 years – 7.4 mcg/day
Skyla 2013 NDA 203159	13.5 mg LNG IUS	3	30 mm x 28 mm	Initial – 14 mcg/day 1 year – 6 mcg/day 3 years – 5 mcg/day
ParaGard T380A 1984 NDA 018680	380 mm^2 exposed copper surface area IUS	10	36 mm x 32 mm	N/A
Nexplanon 2006 NDA 021529	68 mg etonogestrel subdermal implant	3	4 cm x 2 mm	Initial – 60-70 mcg/day 1 year – 35-45 mcg/day 3 years – 25-30 mcg/day

Source: Table Adapted from NDA 21225 S038 Clinical Review, Abby Anderson, MD, May 30, 2017
Abbreviations: IUS, intrauterine system; LNG, levonorgestrel; N/A, not applicable

LNG, the hormonal component of Mirena, has a long history of use in contraception both in the US and worldwide. LNG alone is used orally for emergency contraception and in IUSs. LNG combined with estrogen is available for contraception through oral and transdermal administration.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The FDA approved Mirena on December 6, 2000, for intrauterine contraception for up to 5 years of use. An additional indication for the treatment of HMB for women who choose to use an IUS as their method of contraception was approved on October 1, 2009. On June 8, 2017, approval of an efficacy supplement (S-038) resulted in the removal of the statement "recommended for women who have had at least one child" from the Indications and Usage section of the label. On August 20, 2020, approval another sNDA efficacy supplement (S-040) increased the duration of Mirena use for contraception up to 6 years.

On March 26, 2020, the Applicant submitted the final report for the FDA postmarketing requirement (PMR) study entitled, "Study on the Association of Uterine Perforation and IUD Expulsion with Breastfeeding Status at the Time of IUD[1] Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)." On June 6, 2021, the Agency approved the Complete Response to prior approval labeling supplement (PAS) S-036 to incorporate APEX IUD findings of risk of uterine perforation and IUS expulsion associated with breastfeeding and postpartum status at time of IUS insertion.

(b) (6)

On September 9, 2020, the Applicant submitted prior approval labeling supplement S-041 to incorporate new label information derived from a recent investigation of reports describing virilization of the female fetus with in utero exposure to an LNG IUS. Labeling supplement S-041 was approved May 26, 2021.

On October 13, 2020, the Applicant submitted efficacy supplement NDA S-042, which is summarized in this review.

On February 4, 2021, Annual Report-21 was submitted and two ongoing postmarketing surveillance/noninterventional studies in the United States were noted. These studies are not required (postmarketing requirement) or requested (postmarketing commitment) by the FDA. Neither of these two reports were submitted for review with this supplemental application:

- 18693/DBOX 2015/00961: Use of Claims and Electronic Medical Records (EMR) to Assess Trends and Correlates of Quality Measures for Contraceptive Care. Anticipated study report March 31, 2020.
- 19874/OS-US-2017-4198: Associations between LARC utilization and risk factors and occurrence of Preterm Birth: A Historical Cohort Study. Anticipated study report June 30, 2020.

3.2. Summary of Presubmission/Submission Regulatory Activity

A detailed summary of the regulatory activity can be found in the previous review (S-040) (Food and Drug Administration 2020).

Key agreements between the Agency and the Applicant for extension of Mirena use up to (b) (4) years for contraception are:

[1] IUD = intrauterine device. This term is used interchangeably with intrauterine system (IUS)

- Conduct a study to include fertile women in need of contraception who had Mirena in situ for at least 4 years and 6 months but not longer than 5 years and are willing to continue Mirena use for a total of up to (b) (4) years. The study will access contraceptive efficacy and safety.
- Submit an sNDA for use of Mirena up to 6 years (approved under S-040), followed by submission of sNDA for use of Mirena up to 7 years (this submission, [S-042]). (b) (4) , extension for each year will require a minimum of 200 patients remain in the study per year of extended use.
- Recruit a study population that includes women who are using Mirena for contraception and HMB to address the secondary indication of treatment of HMB, . **Note: low enrollment for the HMB subset in MET 18649 precluded any efficacy determination for this secondary indication. Therefore, no change in the duration of use for the HMB indication is proposed. New labeling regarding cycle control/bleeding would only be included by the Applicant if a safety issue was identified.**
- Submit postmarketing data and reports for patients identified who have kept the LNG IUS in place for greater than 5 years and who have had adverse events or pregnancies.
- Submit a pediatric study plan because the extension for use of Mirena up to 7 years triggered the Pediatric Research Equity Act (PREA).

3.3. Postsubmission Communication

During the review process, the occurrence of postmarketing reports of IUS breakage and hormone reservoir movement on and off the T-body were evaluated in the context of extended Mirena use up to 7 years. With input from the Center for Devices and Radiologic Health (CDRH) and Office of Product Quality (OPQ), information related to these breakage occurrences was requested from the Applicant. The Applicant provided responses to question from CDRH on June 4, 2021. CDRH and the review team evaluated the Applicant's responses and the data on Mirena IUS breakage. There was no signal of increasing breakage trends as duration of use increased and the Applicant's responses were considered acceptable to extend use of Mirena up to 7 years. See Section 4.4 and Appendix for more detailed discussion.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

For the review of this efficacy supplement, clinical site inspections were not required.

4.2. Office of Product Quality (OPQ)

OPQ provided a Review of Chemistry, Manufacturing and Controls (CMC) for the Mirena IUS and concluded the efficacy supplement S-042 is approved from CMC perspective.

In support of the extension of use request for Mirena (21225/S-042) from 6 years to up to 7 years, the Applicant provided (1) in vitro release data for 6 years to 8 years reviewed by Biopharmaceutics and found to exhibit similar drug release profiles over the 8 year period; (2) photographs of ex vivo and unused IUSs and video measurements of the hormone reservoir demonstrating integrity of the membrane; (3) physical and analytic testing of ex vivo IUSs to confirm the long term integrity of the IUS component (T-body and removal thread); (4) breaking force and flexibility of horizontal arms assessed by CDRH and found adequate for extension of use; and (5) information related to polymer stability with test results within the range compared to retained and current samples.

4.3. Clinical Microbiology

For review of this efficacy supplement, Clinical Microbiology consultation was not needed.

4.4. Devices and Companion Diagnostic Issues

A separate consult was requested from CDRH to address the occurrence of IUS breakage and sliding of the hormone reservoir on and off the Mirena T-body reported in the submitted postmarketing reports for patients who used Mirena for greater than 5 years. CDRH reviewed the Applicant's response to an information request for additional information on T-body breakage and movement of the hormone reservoir during device removal (Bayer HealthCare Pharmaceuticals 2021b).

> The June 30, 2021 CDRH memorandum (Price 2021) concludes:
> "Although I defer to the clinical review team for determining the clinical significance of these reported events, based on the firm's calculation, the frequency of events related to the hormone reservoir are rare (or "improbable" as per ISO 14971). In addition, from the information provided there is no "clustering" of the issues around a certain time period or worsening over time."

The CDRH consultant requested further follow up assessment of drug (b) (4) and membrane specifications and tensile strength which are ongoing as part of an overall review of devices, and not considered integral to this efficacy supplement (S-042). See Appendix for details.

4.5. Office of Surveillance and Epidemiology (OSE)

The Division of Pharmacovigilance II, within OSE, updated a previous July 2018 memorandum on device breakage identified in the FDA Adverse Event Reporting System (FAERS) database during this review cycle. The updated memorandum (Chehab 2021) included all FDA-approved IUSs. Only findings related to Mirena use are presented here.

The DPV II Review findings of the FAERS cases of device breakage with Mirena included:

- The proportion of preferred term (PT) device breakage of the total number of adverse event reports was stable from 2013-2019, ranging 1.7-2.6%. A slight increase to 4.4% was noted in 2020. A potential contributing factor for this increase includes increased IUS use amongst women in the US, with Mirena accounting for the majority of the market share during this time.
- Breakage occurred predominately upon removal. Some type of difficulty or resistance with removal was reported in approximately 50% of cases with device breakage.
- No obvious patterns of concern were identified based on lot numbers of the device.

A random sampling of approximately 10% of the total reports of breakage for the 2018 and 2021 memorandums and the case characteristics are presented in the Table 3 below:

Table 3. Case Characteristics of Device Breakage With Mirena in Random Sampling Case Series

Table 8. Case Characteristics of *Device Breakage* with Mirena in this Random Sampling Case Series, Received by FDA from December 6, 2000 - April 30, 2021 (n=185)			
	2018 Memorandum n=130	2021 Memorandum n=55	Cumulative n=185
Reason/identification of breakage	(n=116)	(n=47)	(n=163)
Upon removal	105	38	143
Upon insertion	7	6	13
Spontaneous	3	1	4
Upon expulsion	-	2	2
After sexual intercourse	1	-	1
Type of breakage reported*	(n=130)	(n=55)	(n=185)
String(s) broken/missing	48	23	71
Broken/broken piece/part (not specific)	33	16	49
One arm broken/missing	25	6	31
Both arms broken/missing	21	5	26
Drug reservoir broken/missing*	5	7	12
Loop at end of stem broken	4	2	6
Insertion tube bent/broken/separated	1	-	1
Flange from inserter broken	-	1	1
Inserter broken	-	1	1
Approximate duration of use/time to the identification of breakage	(n=109)	(n=39)	(n=148)
< 1 year	20	6	26
1 year	15	2	17

Table 8. Case Characteristics of *Device Breakage* with Mirena in this Random Sampling Case Series, Received by FDA from December 6, 2000 - April 30, 2021 (n=185)

	2018 Memorandum n=130	2021 Memorandum n=55	Cumulative n=185
2 years	9	3	12
3 years	11	4	15
4 years	16	6	22
5 years	29	6	35
6 years	1	3	4
7 years	1	-	1
10 years	-	2	2
12 years	-	1	1
Upon insertion	7	6	13
Reporter type‡	(n=130)	(n=54)	(n=184)
Healthcare Professional	82	44	126
Consumer	27	10	37
Attorney	21	-	21

* One case may have reported more than one type of breakage.
† The approximate duration of use/time to identification of breakage in the 12 cases of *drug reservoir broken/missing* are < 1 year (n=2), 1 year (n=1), 2 years (n=2), 3 years (n=1), 4 years (n=2), 5 years (n=1), 6 years (n=1), and not reported (n=2). All 12 cases were identified upon removal.
‡ The term *Healthcare Professional* includes certified nurse midwives, medical assistants, nurses, nurse practitioners, physicians, physician assistants, and those not otherwise specified.

Source: Office of Surveillance and Epidemiology, Pharmacovigilance II Memo, Device Breakage, OSE RCM# 2018-892, dated June 14, 2021.

Of importance, there is no clear trend of Mirena IUS breakage based on years of use. The increased number of device breakage at 5 years and less than 1 years most likely reflects when Mirena is removed or inserted, respectively. Given the information available at the time of this review, it supports extension of use of Mirena to 7 years duration.

The Division of Medication Error Prevention and Analysis (DMEPA) assessed the supplement label and found the proposed revision to the Mirena IUS label acceptable (Baugh 2021).

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Mirena is an IUS approved for intrauterine contraception for up to 6 years and for the treatment of heavy menstrual bleeding in women who choose to use intrauterine contraception as their method of contraception. This supplement proposes to extend the use of Mirena for intrauterine contraception up to 7 years. At the time of initial insertion, Mirena contains 52 mg levonorgestrel, to be released at a daily rate of 20 mcg/day. Submitted clinical data suggest that at the end of 7 years, the residual LNG content is approximately 16 mg, or about 30% of the initial LNG content. The in vivo LNG release rate after 7 years of use decreases to 8.1 mcg/day.

There were no nonclinical studies submitted, and none are necessary to extend use of Mirena. There are no nonclinical concerns or issues regarding the safety of continued or extended use of Mirena IUS and the supplement is approvable from the nonclinical perspective.

5.2. Referenced NDAs, BLAs, DMFs

None.

6. Clinical Pharmacology

6.1. Executive Summary

The Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology has reviewed the information contained in the supplemental new drug application (sNDA) and recommends approval of Mirena® for prevention of pregnancy for up to 7 years.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

No dedicated clinical pharmacology study was conducted for the current submission. The Applicant collected blood samples to determine LNG and sex hormone binding globulin (SHBG) concentrations at several time points during the study. In addition, residual contents of LNG were measured in removed devices from 67 women who had their Mirena removed between 6 and 721 days after Day 1 Year 6. Based on LNG and SHBG concentrations as well as residual content measurements from this study, the Applicant conducted population pharmacokinetics (popPK) analysis to characterize the PK of LNG and the LNG in vivo release rates over 7 years of Mirena use.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Mirena® contains 52 mg LNG. The initial release rate is approximately 20 mcg/day over the first 3 months (day 0 to day 90). It is reduced to approximately 18 mcg/day after 1 year, 10 mcg/day after 5 years, and 8 mcg/day after 7 years.

Therapeutic Individualization

N/A

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

In the Phase 3 MET study (Mirena Extension Trial; protocol 18649), sparse blood samples were collected in a subset of subjects to determine LNG and SHBG concentrations after 6, 6.5 and 7 years of Mirena use (Table 4).

Table 4. Measured LNG and SHBG Concentrations (Arithmetic Mean ± SD) in MET Trial

Year	LNG (pg/mL)	SHBG (nM)	N (%*)
6 years	121±50	48±25	144(80)
6.5 years	110±42	47±22	137(76)
7 years	107±40	46±23	95(52)

Data source: Table 14.4/3 and Table 14.4/4 in clinical study report PH-41316
* % of maximum number of samples
Abbreviations: LNG, levonorgestrel; MET, Mirena Extension Trial; SD, standard deviation; SHBG, sex hormone binding globulin

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. After 7-years use of Mirena, the LNG residual content, predicted mean total LNG concentrations, and predicted release rate of LNG from the device were all higher than observed for Kyleena after 5 years of use, and for Skyla after 3 years of use, thus providing supportive evidence that the device can be effective for up to 7 years.

LNG residual content data obtained from Mirena devices collected from women who discontinued prematurely during Years 6 and 7 of Mirena showed the expected remaining LNG content with approximately 25 mg (during the first month of Year 6), 19.6 mg at the end of Year 6 and a minimum of 15.6 mg at the end of Year 7. The residual content after 5 years was similar to earlier residual content measurements.

To support the extension for Mirena use beyond 6 years, the Applicant reevaluated plasma LNG and serum SHBG concentrations and LNG in vivo release rate in an updated modeling and simulation analysis report (R-13456) by including available 7-year data. The maximum Mirena use was 7.08 years.

Based on the updated population PK analysis, the geometric mean total LNG concentrations estimated after 5 years with Mirena (approximately 124 pg/mL) are consistent with total LNG concentrations obtained from earlier analyses and decline slightly during Year 6 and 7 to about 106 pg/mL after 7 years of use. These concentrations are above the estimated mean concentrations observed for Kyleena after 5 years of use (approximately 85 pg/mL) and for Skyla after 3 years of use (approximately 58 pg/mL).

The geometric mean of estimated unbound LNG concentrations decreases from 2.88 pg/mL at 15 days after insertion to 1.93 pg/mL at 5 years, and to 1.66 ng/L at 7 years of treatment.

Mean SHBG concentrations estimated at 5, 5.5, 6, 6.5 and 7 years with Mirena (42.2 to 42.7nM) are similar to SHBG concentrations obtained from earlier analyses starting at 1 year after insertion (between 40 to 50nM), indicating a stable SHBG concentration during continued

Mirena use. Additionally, these SHBG concentrations are similar to those observed after the use of Kyleena and Skyla.

The estimated in vivo release rate for Mirena was estimated to be around 10.7 µg/day after 5 Years, decreasing to 8.1 µg/day after 7 years. The release rate of Mirena after 7 years of use was higher than that of Kyleena after 5 years of use (approximately 7.6 µg/day) and distinctly higher than that of the 3-year product Skyla after 3 years of use (approximately 5.5 µg/day).

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

N/A

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

N/A

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

N/A

Are the bioanalytical assays for LNG and SHBG acceptable?

Yes. The same bioanalytical methods used to determine LNG and SHBG concentrations in Year 6 and Year 7 of Mirena use in Phase 3 MET study. These methods have been reviewed under efficacy supplement of Mirena for prevention of pregnancy for up to 6 years (Supplement 40 approved on August 20, 2020) and were deemed acceptable.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant is conducting a single, open-labeled, phase 3 trial in the US to assess the efficacy and safety of Mirena during extended use beyond 5 years. The trial commenced in December 2016 and is ongoing (up to 8 years). This efficacy submission (S-042) includes data through Year 7 (Month 24 of study).

Table 5. Mirena Extension Trial (MET)

Category	Details
Trial number/title	18649/Multicenter, open-labeled, uncontrolled study to assess contraceptive efficacy and safety of Mirena during extended use beyond 5 years in women 18-35 years of age, including a subgroup evaluation of treatment effect on heavy menstrual bleeding (Mirena Extension Trial) (MET)
NCT number	NCT02985541
Trial design Number of sites	Phase 3, multicenter, open-label, uncontrolled study 61 US study sites 52 US study sites
Study period	December 22, 2016 to May 27, 2020 (last visit for Year 7)
Trial population	• Fertile 18–35-year-old women who were using Mirena for contraception or for contraception and heavy menstrual bleeding. • Duration of use of Mirena at least 4 years 6 months but not more than 5 years • Willing to continue Mirena use for contraception or contraception and HMB for up to 8 years in total
Treatment duration	Up to 3 years (total use of Mirena up to 8 years)
Number of subjects	362
Trial endpoints	Primary Efficacy: Contraceptive efficacy (Pearl Index) Secondary Efficacy: Menstrual blood loss (MBL) in women using Mirena for contraception and HMB (HMB subgroup) Safety: • Adverse events (AE) • AEs of special interest (AESI) - Expulsions - Perforations - Pelvic inflammatory disease (PID) • Other safety - Clinical laboratory - Cervical smear - Chlamydia test - Vital signs, body weight and body mass index (BMI) - Gynecological examination • Uterine bleeding Other: • Pharmacokinetics • Residual LNG content analysis • Post-treatment pregnancy tracking and return to fertility • Subject satisfaction • Ease and pain during Mirena removal

Source: Submission NDA 21225, SDN 1800, Study Report PH-41316, Synopsis p2 of 10
Abbreviations: LNG, levonorgestrel

7.2. Review Strategy

The review strategy for this efficacy supplement (S-042) to extend Mirena's duration of use for contraception up to 7 years included a review of the following data sources and analyses of results from the Applicant. The previous review for Mirena duration of use for contraception up to 6 years (S-040) was approved August 20, 2020 (Food and Drug Administration 2020).

Efficacy:

- NDA efficacy data from trial 18649, MET in the study report PH-41316 for Years 6 and 7
- NDA summary of clinical efficacy

Safety:

- NDA safety data from trial 18649, MET in the study report PH-41316 for Years 6 and 7
- NDA summary of clinical safety
- Supplement: Patients who Used a Single Mirena for >5 Years: Summary of Postmarketing Reports – Supplement with Reports Received between May 9, 2019 and May 8, 2020
- A Division of Pharmacovigilance review of intrauterine systems dated June 14, 2021

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Multicenter, Open-Label, Uncontrolled Study to Assess Contraceptive Efficacy and Safety of Mirena During Extended Use Beyond 5 Years in Women 18 to 35 Years of Age Including a Subgroup Evaluation of Treatment Effect on Heavy Menstrual Bleeding (Mirena Extension Trial)(MET)

Trial Design

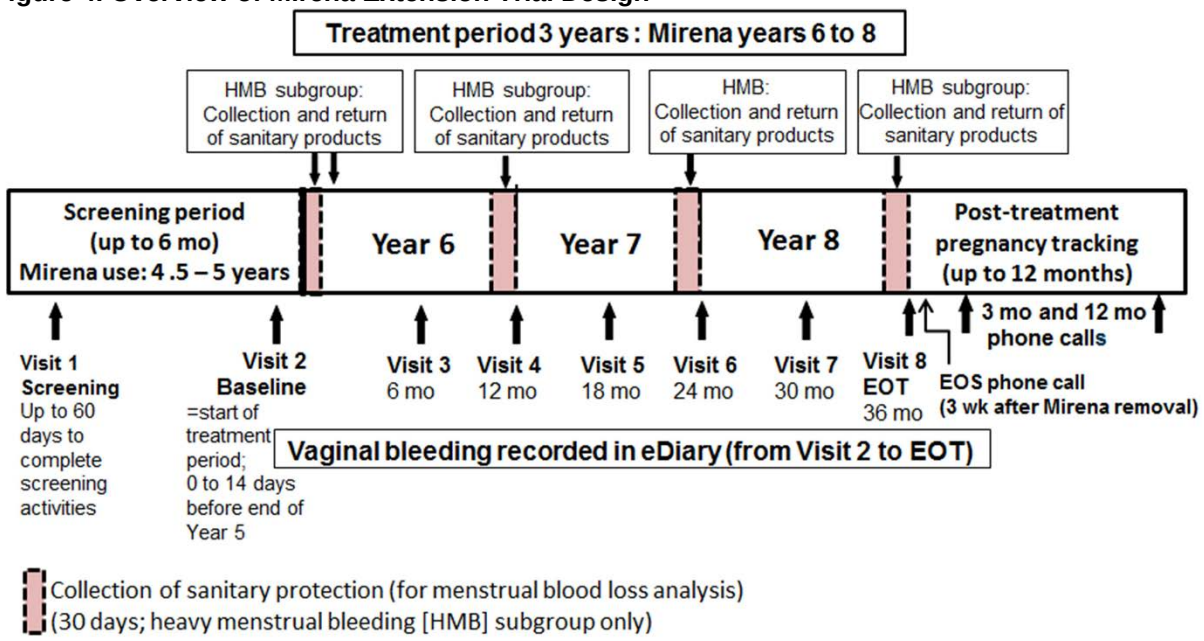
The MET is a phase 3 multicenter, open-label, uncontrolled study in the US to evaluate the contraceptive efficacy and safety of Mirena during extended use for up to 8 years, with analysis at Years 6, 7, and 8. For women who have used Mirena for contraception and HMB, the study will additionally evaluate the stability of effect on menstrual blood loss in Years 6, 7, and 8. The study enrolled women who had used Mirena for contraception or contraception and HMB for up to five years.

The primary efficacy objective is to assess contraceptive efficacy (PI) of Mirena beyond 5 years and up to 8 years of use in women who have been using Mirena for contraception up to 5 years. The secondary efficacy objective was to assess MBL beyond 5 years and up to 8 years of use in women who had Mirena inserted for contraception and HMB (HMB subgroup). Due to low numbers of enrollment for the contraception and HMB subgroup (six women), the Applicant does not propose to use the data from this study extend the duration of use for the HMB indication.

Other study endpoints include safety assessments; evaluation of pharmacokinetics and in vivo release rates of LNG; post treatment return to fertility; user satisfaction and ease and pain during Mirena removal (exploratory).

Figure 4 provides an overview of the trial design for the MET.

Figure 4. Overview of Mirena Extension Trial Design



Source: Submission NDA 21225, SDN 1800, Study Report PH-41316, Figure 7-1 p22 of 1436
Abbreviations: EOS, end of study; EOT, end of treatment; HMB, heavy menstrual bleeding; mo, months; wk, weeks

Trial Conduct

Eligible women were 18 to 35 years of age at the time of screening and were using Mirena either for contraception or for contraception and HMB for at least 4 years 6 months but not more than 5 years. Additional eligibility criteria included willingness to continue Mirena use, continuing need for contraception, and written documentation of date and indication of Mirena insertion. All eligible women, including the HMB subgroup, contribute to the contraceptive efficacy data. Key enrollment criteria are listed in the previous review (Food and Drug Administration 2020).

There are three study periods:

- The screening period included verification of eligibility and presence of Mirena removal threads, dispensation of eDiary for documentation of uterine bleeding and use of backup contraception, and dispensation of alkaline hematin kits to women using Mirena for HMB.
- The treatment period lasts up to 36 months with clinic visits every six months to assess Mirena compliance and safety variables.
- The follow-up period lasts up to 12 months for women who desire pregnancy.

See the previous review for a more detailed discussion of study conduct (Food and Drug Administration 2020).

The study was conducted according to the final approved protocol, dated August 3, 2016, and the amended protocol (version 2.0) dated September 20, 2017.

Schedule of Study Procedures

The study activities and evaluations are summarized in Table 6.

Table 6. Schedule of Trial Activities and Evaluations

Period	Screening (0 to 6 mo)			Treatment Period (3 Years; Mirena Years 6 Thru 8)						Pregnancy Follow-Up (up to 12 mo)		
Visit[a]	Prescreening Contact (Optional)	Screening	Baseline					* Shaded visit is not covered in this report	EOT[b]	EOS All Women	3-mo Contact[c]	12-mo Contact[d]
Visit number	☎/✉	1	2	3	4	5	6	7	8	☎	☎	☎
Timing		Within 60 days	Day 1 -14 d	6 mo ±14 d	12 mo ±14 d	18 mo ±14 d	24 mo ±14 d	30 mo ±14 d	36 mo -14 d	3 wks After EOT -3 d	3 mo After EOT -7 d/ +14 d	12 mo After EOT +7 d
Duration of Mirena use		4 y 6 mo to 5 years	5 years[e]		6 years		7 years		8 years			
Informative discussion about the study/ Distribution of subject information	X	X										
Informed consent		X										
Indication for Mirena and date of insertion		X										
In-/exclusion criteria		X	X									
Demography		X										
Age at baseline			X									
Substance use – Tobacco		X										
Alcohol consumption		X										
Reproductive and menstrual history		X										
Medical history		X										
Physical examination		X			X		X		X			
Vital signs, body weight		X+height			X		X		X			
Gynecological exam. incl. breast palpation		X			X		X		X			
Checking of Mirena threads		X	X	X	X	X	X	X	X			
Cervical smear[f]		X							X			
Chlamydia test[g]		X										
Urine pregnancy test[h]		X	X	X	X	X	X	X	X	X[h]		
Safety laboratory and urinalysis		X			X		X		X			
FSH		X										
Blood sample for PK[i]			X	X[j]	X[j]	X[j]	X[j]		X			
Concomitant medications		X	X	X	X	X	X	X	X			
Adverse events		X	X	X	X	X	X	X	X			
Continuing need for contraception				X	X	X	X	X	X			
Dispense home pregnancy test kits			X	X	X	X	X	X	X			
eDiary dispensed / collected			X						X			

Period	Screening (0 to 6 mo)		Treatment Period (3 Years; Mirena Years 6 Thru 8)						Pregnancy Follow-Up (up to 12 mo)		
Visit[a]	Prescreening Contact (Optional)	Screening	Baseline	* Shaded visit is not covered in this report					EOT[b]	EOS All Women	3-mo Contact[c]	12-mo Contact[d]
Visit number	☎/✉	1	2	3	4	5	6	7	8	☎	☎	☎
Timing		Within 60 days	Day 1 -14 d	6 mo ±14 d	12 mo ±14 d	18 mo ±14 d	24 mo ±14 d	30 mo ±14 d	36 mo -14 d	3 wks After EOT -3 d	3 mo After EOT -7 d/ +14 d	12 mo After EOT +7 d
Duration of Mirena use		4 y 6 mo to 5 years	5 years[e]		6 years		7 years		8 years			
Back-up contraception (if used; eDiary)			→	→	→	→	→	→	→			
Record uterine bleeding (daily, eDiary)			→	→	→	→	→	→	→			
Review of bleeding diary with the woman				X	X	X	X	X	X			
Subject satisfaction with Mirena			X		X		X		X			
Mirena removal									X			
Mirena removal: ease and pain assessment									X			
Documentation of pregnancy/return to fertility										X	X	X

Source: Submission NDA 21225, SDN 1800, Study Report PH-41316, Table 7-1 p28 of 1436

[a] Except the End-of-Treatment (EOT) (Visit 8), visits could also be performed via phone (see Section 6.4.1 of the study protocol).

[b] EOT visit was to be performed also for all women who discontinued treatment. If a woman prematurely discontinued treatment, all efforts were to be made to perform all the assessments scheduled for this EOT visit (Visit 8) including the EOS phone contact 3 weeks after the removal of Mirena before the woman was to be withdrawn from the study.

[c] For women who prematurely discontinued study treatment, unless the reason for discontinuation was "pregnancy", "death", or "withdrawal by subject", where the woman had withdrawn main consent during study conduct and wished to stop future contact with the site. Women that had withdrawn consent during study, but consented to post study participation, follow-up contact was to be made at this point. See also Section 7.4.3.1.

[d] Women that prematurely discontinued treatment due to 'Wish for pregnancy' were to be contacted. If a woman was not pregnant at 3-month contact and no longer wished to become pregnant, a 12-month contact was not required. If a woman was "Lost to Follow-up" at 3-month contact, a 12-month contact was required. See also Section 7.4.3.1.2.

[e] The baseline visit (Visit 2) was to take place 14 to 0 days before the end of Year 5 of Mirena use.

[f] A cervical smear was to be taken at the screening visit or a documented normal result obtained no more than 6 months before screening. Women with ASCUS could be included if they had an HPV DNA test that, according to the standards of the central or local laboratory, was negative for high-risk HPV strains. A single repeat test was permissible if the screening results were abnormal.

[g] If chlamydia test was positive, also tested for gonorrhea. A single repeat test was permiss ble if the screening results were positive.

[h] In addition to the urine pregnancy tests performed by the site at each study visit, women were given home urine pregnancy tests to be used whenever a pregnancy was suspected. Women had to contact the study site immediately if a pregnancy test was positive. Home pregnancy test was to be done on the day of the 3-week contact.

[i] PK sampling: All women: one sample was to be taken at baseline and at EOT (or if the woman prematurely discontinued prior to removal) per woman; and two randomized samples were to be taken at two of the Visits 3 – 6.

[j] PK sampling for women randomized to this visit.

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; d, day; DNA, deoxyribonucleic acid; EOS, end of study; EOT, end of treatment; FSH, follicle-stimulating illoma virus; mo, month; PK, pharmacokinetics; wks, weeks; y, year

Study Endpoints

Efficacy

The primary efficacy endpoint for the contraceptive indication in this submission is the 2-year pregnancy rate (Years 6 and 7) estimated by the Pearl Index (PI), an estimation of the number of unintended pregnancies per 100 woman-years (WY) of exposure. The cumulative failure rate based on life table analysis using the Kaplan-Meier method is calculated as a supportive analysis.

The secondary efficacy endpoints of MBL for Years 6 and 7 are based on daily eDiary bleeding entries and sanitary products collected during three 30-day periods, one at the beginning of Year 6 and one each at the end of Year 6 and Year 7 (see Figure 4). The endpoints only assess women in the HMB subgroup (women who had Mirena inserted for contraception and HMB).

The endpoints are:

- Cumulative MBL expressed as the change of MBL from beginning of Year 6 to the end of Year 7
- Proportion of women with clinical change in bleeding profile regarding HMB defined as blood loss of ≥80 mL

Statistical Analysis Plan

Analysis Sets

The following analysis population were defined in the protocol:

Full Analysis Set (FAS):

- All women who completed the baseline visit of the study.

Primary Analysis Set Year 6 (PAS Year 6)

- All women in the FAS with an age of 35 years or younger at baseline visit (i.e., an age of 36 or younger at end of Year 6).

Primary Analysis Set Year 7 (PAS Year 7)

- All women in the FAS with an age of 34 years or younger at baseline visit ((i.e., an age of 36 or younger at end of Year 7).

Safety Analysis Set (SAF)

- All women who completed the baseline visit of the study.

For determination of effectiveness, the PAS year 7 was the primary dataset. As there were no women of age ≥36 at baseline, FAS, PAS Year 6, and SAF populations (N=362) were identical. Among women in the FAS, nine women were excluded from the PAS Year 7 population (N=353) because they were older than 34 years at baseline visit (i.e., >36 at the end of Year 7).

Data Rules Regarding Calculation of Crude Exposure Time

Per the statistical analysis plan (SAP), the rules regarding the calculation of crude exposure time in days are displayed in Table 7.

Table 7. Definition of Crude Exposure Times

PI	Reason for end of study/ continuation status	Crude exposure time
1-year PI (6th year)	Total expulsion	Date, when expulsion was discovered – Date of Day 1 Year 6 +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – Date of Day 1 Year 6 +1
	Pregnancy	Date of conception – Date of Day 1 Year 6 +1
	Lost to Follow-up	Maximum of (Date Mirena last known in situ – Date of Day 1 Year 6 +1; 1 day)
	Continues into 7th year of treatment	365 days
2-year PI (6th and 7th year)	Total expulsion	Date, when expulsion was discovered – Date of Day 1 Year 6 +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – Date of Day 1 Year 6 +1
	Pregnancy	Date of conception – Date of Day 1 Year 6 +1
	Lost to Follow-up	Maximum of (Date Mirena last known in situ – Date of Day 1 Year 6 +1; 1 day)
	Continues into 8th year of treatment	730 days

Source: Table 6-1 in the Statistical Analysis Plan
Abbreviation: PI, Pearl Index

Handling of Missing Data

Refer to the previous clinical review for Mirena duration of use for contraception up to 6 years (S-040) regarding the details of missing data handling (Food and Drug Administration 2020).

Efficacy Evaluation

For the analysis after 7 years of Mirena use, the primary efficacy endpoint defined by the Applicant is the pregnancy rate measured by the Pearl Index (PI) within Year 6 through 7 of Mirena use (i.e., 2-year PI, as defined below) in PAS Year 7 (i.e., women who were ≤34 years of age at baseline).

Per the SAP, the primary and sensitivity analysis of 2-year PI were as follows:

$$\text{Pearl Index} = \frac{\text{number of on-treatment pregnancies}}{\text{evaluable exposure time}} \times 100$$

where:

- "[O]n-treatment pregnancy" was defined as pregnancies with a date of conception that occurred during the sixth and seventh year of treatment within 7 days after the end of exposure as well as pregnancies that occur after partial expulsion or first occurrence of non-compliance but before Mirena removal were counted.
- "[E]valuable exposure time" was defined for primary and sensitivity analyses of 2-year PI separately.
  - Primary analysis: complete and incomplete 28-day cycles in which no backup contraception was used based on eDiary data.
  - Sensitivity analysis: complete 28-day cycles in which no backup contraception was used based on eDiary data.

Given that the usual assumption for the calculation of PI is a constant hazard for the event of becoming pregnancy over time and this assumption cannot necessarily be held for the study treatment of this study, the PIs per year (i.e., PIs in Year 6 and Year 7 separately) are also be calculated as sensitivity analyses.

In addition to the point estimates for the PIs, two-sided 95% confidence intervals (CIs) based on Poisson distribution are provided.

Life table analysis using Kaplan-Meier method was conducted as a supportive efficacy analysis to estimate the 2-year cumulative pregnancy rate. The exposure time for the life table analyses using Kaplan-Meier method did not exclude the periods of backup contraception use.

All 2-year PIs and cumulative pregnancy rates described above were also evaluated by subgroups of parity, age at baseline, BMI, race, and ethnicity.

As previously stated, the primary efficacy evaluation to determine approvability is based on the efficacy population PAS Year 7. The efficacy evaluation based on the FAS population is also conducted as sensitivity analysis. Subject disposition, demographics, baseline characteristics, protocol deviations, and safety evaluation are based on the safety population FAS/SAF.

Protocol Amendments

One protocol amendment, amendment 1 dated September 20, 2017, was submitted as the integrated clinical study protocol, version 2.0. The protocol and summary of changes were previously reviewed.

The final SAP (v. 1.0) dated October 5, 2017 was last amended (v. 2.0) June 14, 2019.

8.1.2. Study Results

Compliance With Good Clinical Practices

The Certification of Compliance with Requirements of Clinical Trials (form FDA 3674) was completed, signed, and submitted. Study 18649 is being conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonisation/guideline E6: Good Clinical Practice.

The protocol, protocol amendment, and informed consent form were reviewed and approved by each study site's Independent Ethics Committee/Institutional Review Board before the start of the study. The conduct of the clinical study met all local legal and regulatory requirements. The protocol and the amendment were reviewed and approved by the FDA.

Financial Disclosure

No issues with the financial disclosure information were identified. The Certification of Financial Interests and Arrangements of Clinical Investigators (form FDA 3454) is completed, signed, and submitted. Checkbox (1) is marked on form 3454 indicating that none of the investigators entered into any financial arrangement whereby the value of compensation could be affected by the outcome of the study or received significant payments of other sorts as defined in 21 CFR 54.2(f).

An attached tabular listing of investigators indicates a financial certification/disclosure form and disclosure information was collected for all but two investigators. Reasonable efforts by the site to reach the investigators with missing disclosure information were documented.

Patient Disposition

Subject disposition during the MET for Years 6 and 7, separately and overall is summarized in Table 8. A total of 362 women started the treatment and had validated data. Women who completed their end-of-year visit (V4, V6) or End of Treatment visit within certain time parameters were considered "completers." The number of Year 6 "completers" was 296 women (81.8%), although 308 women continued the study into Year 7. The number of Year 7 "completers" was 240 women (66.3%), with 244 women continuing the study into Year 8.

Table 8. Number of Women Who Prematurely Discontinued by Reason and Year (FAS)

Reasons for Premature Discontinuation	Overall Total n (%) N=362[a]	Year 6 n (%) N=362	Year 7 n (%) N=304[b]
Total number of women	118 (32.6)	57 (15.7)	58 (19.1)
Withdrawal by subject	30 (8.3)	16 (4.4)	13 (4.3)
Lost to follow up	23 (6.4)	19 (5.2)	3 (1.0)
Wish for pregnancy	33 (9.1)	9 (2.5)	23 (7.6)
Adverse event	24 (6.6)	10 (2.8)	14 (4.6)
Physician decision	2 (0.6)	1 (0.3)	1 (0.3)
Pregnancy	2 (0.6)	1 (0.3	1 (0.3)
Other	4 (1.1)	1 (0.3)	3 (1.0)

Source: Reviewer's Analysis and Submission NDA 21225, SDN 1800, Study Report PH-41316, Table 8-2, p59 of 1436.
[a] Includes some data from year 8.
[b] One woman did not perform any visit during year 7. She was not reported as discontinued at the time of year 7 database lock and is therefore considered as continuing in the study.
Abbreviations: FAS, full analysis set

Overall, 244 of 362 women (67.4%) enrolled continued into Year 8 (three women had their End of Treatment visit beyond the end of Year 7). Of the 118 women who have discontinued Mirena use prematurely, 56 (32.7%) were nulliparous and 62 (32.5%) were parous. The most common reason for discontinuation was wish for pregnancy (9.1%). The number of women lost to follow up was higher during Year 6 than Year 7 (19 versus 3 women) and the number of women discontinuing for wish for pregnancy and due to an AE were higher during Year 7 than Year 6 (23 versus 9 women and 14 versus 10 women, respectively). Reasons for discontinuation due to physician decision were noncompliance with medications. "Other" reasons for discontinuation were salpingectomy performed, moving and requested new Mirena prior to losing insurance, IUS removal due to ongoing medical history of acne, and patient's disagreement with transfer to another site to continue in this study**.**

Protocol Violations/Deviations

COVID-19 Pandemic

During the conduct of the study, a COVID-19 pandemic/public health emergency (PHE) was declared. The Applicant continued to monitor and manage participant safety during the PHE and concluded that neither the conduct of the study nor the safety results of the study were substantially impacted.

As permitted by the protocol, adjustments or mitigations in study visits and procedures were made by conducting visits via phone and use of home pregnancy tests. Assessments such as checking for removal threads could not be performed remotely. Additionally, the End of Treatment visit (V8) required an on-site clinic visit. If the end of treatment visits could not be conducted due to the PHE restrictions, the visits were postponed until an on-site visit was possible. Women were instructed to use barrier contraception until the clinical visit occurred.

The first study center restrictions due to the PHE were implemented on March 3, 2020, approximately three months before the last patient's last visit for Year 7 interim analyses. Within this three-month time, 54 study visits were to be performed. The Applicant assessed the

impact of missing data on exposure and efficacy endpoints due to the PHE as low and with minimal clinical relevance.

MET Study

At least one protocol deviation was experienced by 312 women (86.2%) in the safety population. Of these women, 130 women (35.9%) had at least one important protocol deviation, e.g., entire study visit not done and 306 women had at least one non-important protocol deviation, e.g., bleeding diary not completed, time schedule deviations. The protocol deviations are tabulated in Table 9.

Table 9. Number of Women With Protocol Deviations (FAS)

Protocol Deviation Category	Contraception N=356 (100%)	Contraception and HMB N=6 (100%)	Total N=362 (100%)
Women with any protocol deviation	306 (86.0%)	6 (100.0%)	312 (86.2%)
Other protocol deviations	284 (79.8%)	5 (83.3%)	289 (79.8%)
Procedure deviations	180 (50.6%)	5 (83.3%)	185 (51.1%)
Inclusion/exclusion criteria not met but woman entered treatment	34 (9.6%)	0	34 (9.4%)
Time schedule deviations	7 (2.0%)	0	7 (1.9%)
Treatment deviations	4 (1.1%)	0	4 (1.1%)
Withdrawal criteria met during treatment but not withdrawn	1 (0.3%)	0	1 (0.3%)
Women with important protocol deviation	125 (35.1%)	5 (83.3%)	130 (35.9%)
Procedure deviations	107 (30.1%)	5 (83.3%)	112 (30.9%)
Inclusion/exclusion criteria not met but woman entered treatment	34 (9.6%)	0	34 (9.4%)
Withdrawal criteria met during treatment but not withdrawn	1 (0.3%)	0	1 (0.3%)
Women with non-important protocol deviation	301 (84.6%)	5 (83.3%)	306 (84.5%)
Other protocol deviations	284 (79.8%)	5 (83.3%)	289 (79.8%)
Procedure deviations	161 (45.2%)	3 (50.0%)	164 (45.3%)
Time schedule deviations	7 (2.0%)	0	7 (1.9%)
Treatment deviations	4 (1.1%)	0	4 (1.1%)

Source: Reviewer's Analysis and Submission NDA 21225, SDN 1800, Study Report PH-41316, Table 8-5 p62 of 1436
Women may have more than one protocol deviation but are only counted once within each deviation category.
Abbreviations: FAS, full analysis set; HMB, heavy menstrual bleeding

The clinical and statistical reviewers concurred that these protocol deviations in the safety population did not contribute to the loss of subjects in the efficacy population or to the loss of evaluable cycles in the PI calculations.

Table of Demographic Characteristics

Demographic characteristics for the FAS and the PAS Year 7 populations are presented in Table 10. From a clinical perspective, the study appears to reflect the population in the US that will use Mirena. Most enrolled women were white (75.4%) and not Hispanic (88%). Nulliparous women made up 47.2% of the population.

Table 10. Demographic or Baseline Characteristics Year 7 (FAS and PAS Yr 7)

Demographic or Baseline Characteristic	FAS N=362	PAS Year 7 N=353
Sex, n (%)		
Female	362 (100)	353 (100)
Age at baseline (years)		
Mean (SD)	29.4 (3.1)	29.2 (3.0)
Median	30.0	30.0
Min, max	19, 35	19, 34
Age group at baseline (years), n (%)		
18–25	41 (11.3)	41 (11.6)
26–35	321 (88.7)	312 (88.4)
Race, n (%)		
White	273 (75.4)	266 (75.4)
Black or African American	51 (14.1)	49 (13.9)
Asian	9 (2.5)	9 (2.5)
American Indian or Alaska Native	2 (0.6)	2 (0.6)
Native Hawaiian or other Pacific Islander	0	0
Multiple	13 (3.6)	13 (3.7)
Not reported	14 (3.9)	14 (4.0)
Ethnicity, n (%)		
Not Hispanic or Latino	319 (88.1)	310 (87.8)
Hispanic or Latino	41 (11.3)	41 (11.6)
Not reported	2 (0.6)	2 (0.6)
BMI (kg/m^2) at screening		
Mean (SD)	27.91 (6.93)	27.89 (6.99)
Median	26.07	25.99
Minimum, maximum	15.4, 57.7	15.4, 57.7
BMI group (kg/m^2) at screening, n (%)		
<30 kg/m^2	248 (68.5)	243 (68.8)
≥30 kg/m^2	114 (31.5)	110 (31.2)
Never smoker, n (%)	254 (70.2)	248 (70.3)
Alcohol use, n (%)	303 (83.7)	297 (84.2)
College degree or equivalent professional qualification, n (%)	248 (68.5)	243 (68.8)

Source: Reviewer's Analysis and Submission NDA 21225, SDN 1800, Study Report PH-41316, Table 8-7 p65 of 1436
Abbreviations: BMI body mass index; FAS, full analysis set; PAS primary analysis set; SD, standard deviation

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Medical and surgical histories were obtained during the screening visit. The most common medical history conditions included anxiety (23.2%), seasonal allergy (21.5%), and depression (19.6%). The most common gynecological procedure history was cesarean section (8.8%). More details on baseline characteristics are presented in the previous review (Food and Drug Administration 2020).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was confirmed by the presence of Mirena threads during pelvic examination at each study visit, or if the Mirena threads could not be verified, by transvaginal ultrasound (TVUS). Treatment compliance at the end of Year 7 (V6) was reported as 98.1% (208 of 212 women). During Year 7 five women exited the study due to noncompliance of IUS

location (2 partial expulsions, 1 total expulsion, 2 partial perforations/embedment). During Year 6 two women exited the study due to two partial expulsions.

All medications taken during the study were recorded in the eCRF. Concomitant medication use during the study was reported in 294 women (81.2%). Medications taken by over 10% of women were ibuprofen (22.4%) and vitamins (12.4%). None of the concomitant medications reported were expected to interfere with the effectiveness or safety of Mirena use.

Efficacy Results – Primary Endpoint

Contraceptive efficacy of Mirena is based on the on-treatment pregnancy rate assessed using the PI calculations (primary) and Life Table analyses using Kaplan-Meier method (supportive). Women over age 36 at the end of Year 7 are excluded from the PI calculations as this was the agreed to cutoff to capture pregnancy rates when women did not have decreased rates of pregnancy from advancing age. Pregnancy is defined as a positive blood or urine pregnancy test (UPT). An on-treatment pregnancy, as defined per protocol, is a pregnancy with reported date of conception during IUS use or within 7 days after IUS discontinuation.

Two on-treatment pregnancies were reported during Years 6 and 7 of Mirena use and included in the pregnancy rate calculations. One on-treatment pregnancy ending in spontaneous abortion occurred during Year 6 and one on-treatment ectopic pregnancy occurred during Year 7 of Mirena use. The narrative for the pregnancy occurring in Year 6 was previously presented during review of Year 6 data (Food and Drug Administration 2020).

During Year 7, a pregnancy occurred in Subject ID # (b) (6), a 26-year-old, who had a negative UPT and visualization of Mirena threads at Visit 5 (Year 6.5) on (b) (6). On (b) (6), she reported breast tenderness, pelvic cramping, and light vaginal bleeding. A home pregnancy test on (b) (6) showed a positive result, which was confirmed at the clinic on (b) (6) with a serum pregnancy test and an elevated hCG (692 U/L). A TVUS performed the same day showed no pregnancy and the IUS was removed. Increasing levels of hCG were found on (b) (6) (758 U/L) and (b) (6) (765 U/L). Treatment with methotrexate was given on (b) (6) and (b) (6). On (b) (6), her serum hCG was negative. Premature discontinuation occurred (b) (6) at her End of Treatment visit. The investigator estimated the date of conception was (b) (6). Although no pregnancy location was confirmed, the gradual rise in serum hCG levels and no findings of pregnancy on TVUS are consistent with a diagnosis of ectopic pregnancy.

Two additional women became pregnant with estimated dates of conception within three weeks of discontinuing use of Mirena. Subject ID# (b) (6) discontinued use of Mirena due to wish for pregnancy. Based on her LMP and an ultrasound, the estimated date of conception was 16 days after Mirena removal. Subject ID# (b) (6) discontinued use of Mirena due to wish for pregnancy. At her 3-week follow up phone call, she reported a negative home pregnancy test. At her 3-month follow up phone call, she had become pregnant and based on her LMP the estimated date of conception was 12 days after Mirena removal. Neither of these pregnancies are considered on-treatment as they were after removal of the IUS product.

The 2-year and yearly PI (6th and 7th year separately) based on the PAS Year 7 are summarized in Table 11. As shown in Table 11, the 2-year PI calculated by the Agency and the Applicant based on the exposure as complete and incomplete 28-day cycles is 0.39 (95% PI: 0.05, 1.42). The Year 6 PI (6th year) and Year 7 PI (7th year) are 0.35 (95% CI: 0.01, 1.95) and 0.45 (95% CI: 0.01, 2.49), respectively.

Table 11. Pearl Index: Primary Analysis Based on Complete/Incomplete 28-Day Cycles (PAS Yr 7)

	N	Number of Pregnancies	Total Time of Exposure [cycles/wy]	Excluded Time of Exposure [cycles/wy]	Evaluable Time of Exposure [cycles/wy]	Pearl Index (95% CI)
2-year (Years 6 and 7)	353	2	7268.84/557.61	623.63/47.84	6645.21/509.77	0.39 (0.05, 1.42)
Year 6	353	1	4107.81/315.12	375.04/28.77	3732.77/286.35	0.35 (0.01, 1.95)
Year 7	291	1	3161.03/242.49	248.72/19.08	2912.44/223.42	0.45 (0.01, 2.49)

Source: Reviewer's Analysis and Clinical Study Report of Study 18649 year 7: Table 14.2.1/2
Note. Total exposure for 2-year (Year 6 and 7) Pearl Index is calculated from Day 1 of Year 6 to Day 730, or to the below date (*) if earlier than Day 730. Total exposure for Year 6 Pearl Index is calculated from Day 1 of Year 6 to Day 365, or to the below date (*) if earlier than Day 365. Total exposure for Year 7 Pearl Index is calculated from Day 1 of Year 7 (i.e., Day 366) to Day 730, or to the below date (*) if later than Day 365 but earlier than Day 730. (*) is the date of conception in case of pregnancy or -if no pregnancy occurred-date of expulsion/removal (in case of expulsion/removal) and date Mirena last known in situ (in case of no expulsion/removal), respectively. Any 28-day reference period of backup contraception was excluded from the exposure time, unless a pregnancy occurred in that 28-day reference period.
Abbreviations: CI, confidence interval; PAS, primary analysis set; wy, woman years (1 wy = 365 days)

As shown in Table 12, sensitivity analysis, based on exposure as completed 28-day cycles, yielded an estimated 2-year PI of 0.40 (95% CI: 0.05, 1.44). The PI estimates from primary and sensitivity analyses based on PAS Year 7 were comparable. Note that the total number of women included in the analysis is different in the primary and sensitivity analysis for Year 7 PI, 291 versus 293 women, respectively. This difference between these calculations is due to the fact that two women contributed data until and including Day 365. In the analysis based on complete and incomplete 28-day cycles, Year 7 starts on Day 366, therefore, these two women are not included in the primary analysis of Year 7 PI. However, in the sensitivity analysis based on complete 28-day cycles, the Year 7 starts on Day 365, and these two women are included in the sensitivity analysis of Year 7 PI.

Table 12. Pearl Index: Sensitivity Analysis Based on Complete 28-Day Cycles (PAS Yr 7)

	N	Subjects With Complete 28-Day Cycles	Number of Pregnancies	Total Time of Exposure [cycles/wy]	Excluded Time of Exposure [cycles/wy]	Evaluable Time of Exposure [cycles/wy]	Pearl Index (95% CI)
2-year (Yrs 6 and 7)	353	333	2	7135.96/548.92	616.98/47.46	6518.98/501.46	0.40 (0.05, 1.44)
Year 6	353	333	1	4073.94/313.38	374.01/28.77	3700.06/284.62	0.35 (0.01, 1.96)
Year 7	293	285	1	3062.02/235.54	242.97/18.69	2819.05/216.85	0.46 (0.01, 2.57)

Source: Reviewer's Analysis and Study 18649 year 7 patient 2 document: Table 16.4.1.2.1/1
Note. Total exposure for 2-year (Year 6 and 7) Pearl Index is calculated from Day 1 of Year 6 to last day of last complete cycle in Year 6 or 7. Total exposure for Year 6 Pearl Index is calculated from Day 1 of Year 6 to last day of last complete cycle in Year 6. Total exposure for Year 7 Pearl Index is calculated from Day 1 of Year 7 (i.e., Day 365) to last day of last complete cycle in Year 7. Any 28-day cycle of backup contraception use was excluded from the exposure time, unless a pregnancy occurred in that 28-day cycle.
Abbreviations: CI, confidence interval; PAS, primary analysis set; wy, woman years (1 wy = 13 cycles of 28 days = 364 days)

The 2-year and yearly PI (6^{th} and 7^{th} year separately) based on the FAS were also conducted as sensitivity analyses. As shown in the Table 13, the 2-year PI calculated by the Agency and the Applicant based on the exposure as complete and incomplete 28-day cycles is 0.38 (95% PI: 0.05, 1.37). The Year 6 PI (6^{th} year) and Year 7 PI (7^{th} year) are 0.34 (95% CI: 0.01, 1.89) and 0.43 (95% CI: 0.01, 2.41), respectively. The estimated 2-year and yearly PI (6^{th} and 7^{th} year separately) based on the FAS (N=362) and PAS Year 7 (N=353) populations were almost numerically the same.

Table 13. Pearl Index: Sensitivity Analysis Based on Complete/Incomplete 28-Day Cycles (FAS)

	N	Number of Pregnancies	Total Time of Exposure [cycles/wy]	Excluded Time of Exposure [cycles/wy]	Evaluable Time of Exposure [cycles/wy]	Pearl Index (95% CI)
2-year (Yrs 6 and 7)	362	2	7490.05/574.58	626.63/48.07	6863.43/526.51	0.38 (0.05, 1.37)
Year 6	362	1	4225.13/324.12	375.04/28.77	3850.09/295.35	0.34 (0.01, 1.89)
Year 7	300	1	3264.92/250.46	251.72/19.31	3013.20/231.15	0.43 (0.01, 2.41)

Source: Reviewer's Analysis and Clinical Study Report of Study 18649 year 7: Table 14.2.1/1
Note. Total exposure for 2-year (Year 6 and 7) Pearl Index is calculated from Day 1 of Year 6 to Day 730, or to the below date (*) if earlier than Day 730. Total exposure for Year 6 Pearl Index is calculated from Day 1 of Year 6 to Day 365, or to the below date (*) if earlier than Day 365. Total exposure for Year 7 Pearl Index is calculated from Day 1 of Year 7 (i.e., Day 366) to Day 730, or to the below date (*) if later than Day 365 but earlier than Day 730. (*) is the date of conception in case of pregnancy or -if no pregnancy occurred-date of expulsion/removal (in case of expulsion/removal) and date Mirena last known in situ (in case of no expulsion/removal), respectively. Any 28-day reference period of backup contraception was excluded from the exposure time, unless a pregnancy occurred in that 28-day reference period.
Abbreviations: CI, confidence interval; PAS, primary analysis set; wy, woman years (1 wy = 365 days)

Table 14 presents the 2-year cumulative pregnancy rate based on both the Mirena PAS Year 7 and FAS populations based on life table analysis using Kaplan-Meier method with no periods of backup contraception use excluded. The estimated 2-year cumulative pregnancy rates were the same between the Applicant and FDA analysis. As shown in Table 14, the 2-year cumulative pregnancy rates estimated by life table analysis using Kaplan-Meier method based on PAS Year 7 and FAS respectively were comparable to each other (0.71 versus 0.69), and they were

numerically slightly higher than the 2-year PI estimates (PAS Year 7: 0.71 versus 0.39; FAS: 0.69 versus 0.38).

Table 14. 2-Year Cumulative Pregnancy Rate - Life Table Analysis Using Kaplan-Meier Method

	N	Number of Pregnancies	Evaluable Exposure (cycles/wy)	Probability (%) (95% CI)
PAS Year 7	353	2	7268.84/557.61	0.71 (0.17, 2.84)
FAS	362	2	7490.05/574.58	0.69 (0.17, 2.76)

Source: Reviewer's Analysis and Clinical Study Report of Study 18649 year 7: Table 9-9 and Table 14.2.1/19
Note. Total exposure for 2-year (Year 6 and 7) probability is calculated from Day 1 of Year 6 to Day 730, or to the date of conception in case of pregnancy or -if no pregnancy occurred- date of expulsion/removal (in case of expulsion/removal) and date Mirena last known in situ (in case of no expulsion/removal), respectively, if earlier than Day 730.
Abbreviations: CI, confidence interval; FAS, full analysis set; PAS, primary analysis set; wy, woman years (1 wy = 365 days)

Subgroup Analysis

Table 15 presents 2-year PIs by age at baseline, parity, BMI, race, and ethnicity based on the PAS Year 7 population. Table 16 presents the cumulative 2-year pregnancy rate by the same subgroups in the PAS Year 7 population based on life table analysis using Kaplan-Meier method. Similar to the life table analysis using Kaplan-Meier method on the overall population, the periods of backup contraception use were not subtracted from the exposure time for the subgroup life table analysis using Kaplan-Meier method.

Clinical Reviewer Comment: Due to the small number of pregnancies (n=2), the pregnancy rate estimation by subgroups is for presentation purpose only.

Table 15. 2-Year Pearl Index by Subgroup (PAS Yr 7)

Subgroup	N	# of Pregnancies	Evaluable Exposure (cycles/wy)	Pearl Index	Lower 95% CI	Upper 95% CI
Age at baseline						
18-25 years	41	1	663.00/50.86	1.97	0.05	10.95
26-35 years	312	1	5982.21/458.91	0.22	0.01	1.21
Parity						
Nulliparous	171	2	3193.23/244.96	0.82	0.10	2.95
Parous	182	0	3451.98/264.81	0.00	0.00	1.39
BMI (kg/m^2)						
<30	243	2	4543.33/348.53	0.57	0.07	2.07
≥30	110	0	2101.88/161.24	0.00	0.00	2.29
Race						
White	266	2	4999.84/383.55	0.52	0.06	1.88
Black or African American	49	0	921.75/70.71	0.00	0.00	5.22
Asian	9	0	170.90/13.11	0.00	0.00	28.14
American Indian or Alaska Native	2	0	36.24/2.78	0.00	0.00	132.79
Multiple	14	0	277.27/21.27	0.00	0.00	17.34
Not reported	13	0	239.21/18.35	0.00	0.00	20.10

Subgroup	N	# of Pregnancies	Evaluable Exposure (cycles/wy)	Pearl Index	Lower 95% CI	Upper 95% CI
Ethnicity						
Not Hispanic	310	2	5844.03/448.31	0.45	0.05	1.61
Hispanic	41	0	772.37/59.25	0.00	0.00	6.23
Not reported	2	0	28.81/2.21	0.00	0.00	167.26

Source: Reviewer's Analysis and Clinical Study Report of Study 18649 Year 7: Table 9-8
Note. Total exposure for 2-year Pearl Index is calculated from Day 1 Year 6 (calculated based on the date of Mirena insertion) until Day 730 of Year 7, or to the following date if earlier than Day 730 of Year 7: date of conception in case of pregnancy or – if no pregnancy occurred – date of expulsion/removal (in case of expulsion/removal) and date Mirena last known in situ (in case of no expulsion/removal), respectively. The evaluable time is the total exposure time excluding 28-day reference period(s) of backup contraception use, unless a pregnancy occurred in that 28-day reference period.
Abbreviations: BMI, body mass index; CI, confidence interval; PAS, primary analysis set; wy, women years (1 wy =365 days)

Table 16. 2-Year Cumulative Pregnancy Rate (Life Table Subgroup Analysis) using KM (PAS Yr 7)

Subgroup	N	# of Pregnancies	Exposure (cycles/wy)	Probability (%)	Lower 95% CI	Upper 95% CI
Age at baseline						
18-25 years	41	1	727.78/55.83	2.63	0.37	17.25
26-35 years	312	1	6541.18/501.79	0.45	0.06	3.17
Parity						
Nulliparous	171	2	3550.14/272.34	1.44	0.36	5.75
Parous	182	0	3718.69/285.27	0.00	NA	NA
BMI (kg/m^2)						
<30	243	2	4975.60/381.69	1.04	0.26	4.17
≥30	110	0	2293.37/175.93	0.00	NA	NA
Race						
White	266	2	5460.26/418.87	0.95	0.23	3.79
Black or African American	49	0	1004.66/77.07	0.00	NA	NA
Asian	9	0	176.89/13.57	0.00	NA	NA
American Indian or Alaska Native	2	0	40.15/3.08	0.00	NA	NA
Multiple	14	0	308.82/23.69	0.00	NA	NA
Not reported	13	0	277.92/21.32	0.00	NA	NA
Ethnicity						
Not Hispanic	310	2	6382.93/489.65	0.81	0.20	3.24
Hispanic	41	0	840.15/64.45	0.00	NA	NA
Not reported	2	0	45.76/3.51	0.00	NA	NA

Source: Reviewer's Analysis and Clinical Study Report of Study 18649 Year 7: Table 9-9
Note: Total exposure for 2-year (Year 6 and 7) probability is calculated from Day 1 of Year 6 to Day 730, or to the date of conception in case of pregnancy or -if no pregnancy occurred- date of expulsion/removal (in case of expulsion/removal) and date Mirena last known in situ (in case of no expulsion/removal), respectively, if earlier than Day 730.
Abbreviations: KM, Kaplan Meier; BMI, body mass index; CI, confidence interval; NA, not applicable; PAS, primary analysis set; wy, women years (1 wy =365 days)

Data Quality and Integrity

Data quality and integrity were satisfactory as demonstrated by study assessments and narratives. The number of subject discontinuations and the reasons for subject discontinuation were consistent with contraceptive studies. There were no concerning trends or discrepancies in the submission that raised reviewer concerns.

Efficacy Results – Secondary and Other Relevant Endpoints

Assessment of the secondary efficacy endpoint, MBL in the subgroup of women who used Mirena for both contraception and HMB (HMB subgroup), was not possible due to the low sample size of six women. In the absence of evaluable data on MBL after five years of Mirena use, the indication of treatment of HMB for women who choose to use intrauterine contraception as their method of contraception will remain at up to 5 years.

The Applicant did report descriptive results for four women in the HMB subgroup. Two of the six women prematurely withdrew from the study (withdrawal by subject), one each year. At the end of Year 7, three of the four women had MBL of zero and missing data on the remaining woman did not allow for MBL calculation. Since the beginning of Year 6, none of the six women experienced MBL >80 mL/30 days during the reporting periods.

Dose/Dose Response

Not applicable. For this submission, Mirena was evaluated at a single dose LNG IUS formulation.

Durability of Response

Contraceptive efficacy showed durability of response with Mirena use up to 7 years. The pregnancy rate expressed as PIs for Year 7 and for Years 6 and 7 are 0.45 [95% CI (0.01, 2.49)] and 0.39 [95% CI (0.05, 1.42)], respectively based on the PAS Year 7. The cumulative 2-year pregnancy rate of 0.71% for Years 6 and 7 is consistent with the cumulative 5-year pregnancy rate of approximately 0.7 per 100 women reported in the Mirena label.

Persistence of Effect (Return to Fertility)

The Applicant is assessing return to fertility over time by tracking the time elapsed to pregnancy after Mirena removal in women who discontinue use of Mirena due to desire for pregnancy. These women are followed for up to 12 months to assess fertility. The current database on return to fertility includes 33 women. At the time of data cutoff, 14 pregnancies were reported in this cohort; 10 women have completed the 12-month tracking period.

Additionally, women who discontinued the study because of an AE, withdrawal from study, and wish for pregnancy were contacted at 3 months. Of the 56 women who discontinued the study for the listed reasons, 16 have reported post-treatment pregnancies; 14 of the 16 pregnancies occurred in women who wished for pregnancy.

As return to fertility is an important consideration for providers and patients, this limited information will be labeled with updated findings upon completion of the MET.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Not applicable.

Additional Analyses Conducted on the Individual Trial

Not applicable.

Integrated Review of Effectiveness

Not applicable.

8.1.3. Integrated Assessment of Effectiveness

Findings from the single, open-labeled phase 3 MET study were evaluated to assess the efficacy of Mirena use during Years 6 and 7 for prevention of pregnancy. Therefore, an integrated review of effectiveness is not applicable to this review.

8.2. Review of Safety

8.2.1. Safety Review Approach

Mirena was first approved by the FDA on December 6, 2000 for up to five years of intrauterine contraception and on October 1, 2009 for treatment of HMB for up to 5 years in women who chose to use intrauterine contraception as their method of contraception. On August 20, 2020, Mirena was approved for contraception for up to six years of intrauterine contraception. The indication for treatment of HMB remains for up to 5 years.

In this review, the safety of Mirena use for contraception up to 7 years is based on the first- and second-year findings of the MET (a three-year phase 3 multicentered study in the US to evaluate the contraceptive efficacy and safety of Mirena during extended use for up to 8 years) and supportive safety evidence from a Summary of Postmarketing Reports.

The MET enrolled subjects who had been using Mirena at least 4 years and 6 months (up to 5 years) and were willing to continue Mirena use for contraception for up to 8 years. The MET also includes a subgroup of six (6) women using Mirena for contraception and HMB.

The Summary of Postmarketing Reports is a tabulation and analysis of postmarketing reports in patients who used a single Mirena for more than five years and experienced an AE or pregnancy. This summary is reviewed in Section 8.2.10.

8.2.2. Review of the Safety Database

Overall Exposure

The full analysis set (FAS) population in the MET is composed of 362 women aged 18 to 35 years who were enrolled at the beginning of the trial with verified source data and include Mirena use through Years 6 and 7. The safety analysis set (SAF) population for Years 6 and 7 is identical to the FAS population of 362 women. The SAF population for Year 7 is composed of 304 women.

Cumulative Mirena exposure of the FAS population for Years 6 and 7 is 577.3 WY and 7,524.5 28-day cycles. Women were exposed to an average use of 20.79 cycles during Years 6 and 7. A

total of 240 (66.3%) women completed Years 6 and 7 based on attendance to the month 24 clinic visit (V6) (see Table 6, Schedule of Study Procedures in Section 8.1.1).

Adequacy of the Safety Database

A total of 240 women completed the full 7-year course of treatment, exceeding the requirement of at least 200 subjects completing the proposed duration of use. Total exposure of 7,524 28-day cycles for Years 6 and 7 of Mirena use, is less than the required number of cycles for new contraceptive products. However, LNG IUSs are not new contraceptives and have a known safety profile. The safety database as submitted is deemed adequate for review of Mirena use up to 7 years.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No concerns regarding the reported data integrity and quality are identified. Changes that the Applicant made during the PHE were evaluated and determined to be acceptable. The narratives of reported adverse event reporting, including pregnancy outcomes, are adequate.

Categorization of Adverse Events

The Applicant reports AEs for Year 7 by preferred terms (PT) and system-organ classes (SOC) from MedDRA, version 23.0. The Applicant submitted additional AE summaries for labeling purposes, mapping the Applicant's MedDRA labeling grouping to MedDRA PTs.

AEs were collected at each visit. Treatment-emergent AEs are AEs that occurred on Day 1 of Year 6 of Mirena use or later.

Routine Clinical Tests

Routine clinical evaluations performed through Years 6 and 7 of the MET are comprehensive and consistent with IUS contraceptive trials.

The clinical tests include:

- Clinical laboratory tests – hematology, serum chemistry, urinalysis
- Cervical smear
- Chlamydia test
- Vital signs, body weight, BMI
- Gynecological examination including breast palpation
- Pregnancy tests
- Presence of Mirena

8.2.4. Safety Results

Deaths

No deaths occurred during Years 6 and 7 of Mirena use.

Serious Adverse Events

A total of 10 women experienced 12 serious adverse events (SAE) with onset during Years 6 and 7: five (5) women each year. The overall incidence of SAEs is 2.8%.

The outcomes of the SAEs were resolved at the time of database lock in all but one woman who experienced suicidal ideation. Four women prematurely discontinued the study due to the SAE: Year 6 - spontaneous abortion and Year 7 - ectopic pregnancy, embedded device, and uterine perforation (partial). Of the SAEs related to Mirena use, there were no unexpected adverse events identified.

Table 17 lists the SAEs experienced by women in each year and overall.

Table 17. Number of Women With SAEs Overall and by Year of Onset (SAF)

Preferred Term*	Total Number of Women		
	Overall n (%) N=362	Year 6 n (%) N=362	Year 7 n (%) N=304
Total number of women with at least one SAE	10 (2.8)	5 (1.4)	5 (1.6)
Suicidal ideation	2 (0.6)	1 (0.3)	1[a] (0.3)
Abortion spontaneous	1 (0.3)	1 (0.3)	0
Ectopic pregnancy with contraceptive device	1 (0.3)	0	1 (0.3)
Uterine perforation (partial)	1 (0.3)	0	1 (0.3)
Embedded device	1 (0.3)	0	1 (0.3)
Obesity	1 (0.3)	0	1 (0.3)
Conversion disorder	1 (0.3)	1 (0.3)	0
Cerebellar stroke[b]	1 (0.3)	1 (0.3)	0
Radial nerve palsy	1 (0.3)	1 (0.3)	0
Vertebral artery dissection[b]	1 (0.3)	1 (0.3)	0
Volvulus	1 (0.3)	1 (0.3)	0

Source: Source: Submission NDA 21225, SDN 1800, Study Report PH-41316, Table 10-6 p107 of 1436
* MedDRA Version 23.0

[a] Subject ID# 14039-0006: suicide ideation preceded by suicide attempt. See narrative in Table 18
[b] Subject sustained a neck injury; narrative in previous review (Food and Drug Administration 2020).
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SAF, safety analysis set

Narratives for women experiencing SAEs during Year 7 of Mirena use are summarized in Table 18. Narratives for women experiencing SAEs during Year 6 are summarized in the previous review (Food and Drug Administration 2020) .

Table 18. SAEs With Onset During Year 7 (Narratives)

Subject ID Number Age (Years) Start Relative to Day 1 Year 6	SAE	Narrative
(b) (6) 26 y/o Day 584	Ectopic pregnancy	Presented with breast tenderness, pelvic cramping, and light vaginal bleeding. On (b) (6) serum hCG test result was 692 U/L. TVUS imaging did not show any pregnancy and Mirena was removed the same day. On (b) (6) hCG increased to 758 U/L. On March 1, 2019 hCG increased to 765 U/L. Based on gradual rise of hCG levels and negative TVUS findings, diagnosis of ectopic pregnancy with contraceptive device was made. Mirena removed (b) (6) followed by treatment with methotrexate on (b) (6) Pregnancy resolved. Subject exited study.
(b) (6) 28 y/o Day 500	Embedded device	Experienced ongoing abdominal pain and four months after symptom onset, TVUS imaging showed IUS with myometrial perforation. Event resolved with removal of IUS. Subject exited study.
(b) (6) 26 y/o Day 545	Uterine perforation (partial)	At Visit 5 ((b) (6)), IUS threads were missing. TVUS imaging showed IUS to be adjacent to the cervix with myometrial perforation by the left portion. Previous TVUS imaging for missing threads confirmed IUS was in situ in (b) (6) Mirena removed via the vagina on (b) (6) Event resolved (b) (6) Subject exited study.
(b) (6) 30 y/o Day not calculated (Hospitalization occurred during Year 6, month 5)	Suicidal ideation Suicide attempt Depression	Hospitalized for suicidal thoughts ((b) (6)) which was preceded by attempted suicide (b) (6) and worsening depression since (b) (6) and discontinuation of medications for anxiety and depression (date not provided). History of borderline personality disorder, anxiety, depression, and post-traumatic stress disorder all starting (b) (6) . Event not resolved but Mirena use continued.
(b) (6) 33 y/o Day 534	Morbid obesity	Event of morbid obesity for gastric bypass surgery requiring hospitalization. Weight gain from 234.3 to 258.0 pounds over 17 months. History of gastric lap band surgery 8 years prior. Event resolved. Mirena use continued.

Source: Source: Submission NDA 21225, SDN 1800, Study Report PH-41316, Table 10-7 p 108 and Narratives p1189 of 1436

Dropouts and/or Discontinuations Due to Adverse Effects

A total of 24 women experienced at least one AE leading to early discontinuation of Mirena during Years 6 and 7. Fifteen (15) women discontinued in Year 7 (including two women with AEs beginning in Year 6) and 9 women discontinued in Year 6 (excluding one woman whose AE began in Year 5). The overall incidence of AEs leading to withdrawal is 6.6%.

Three of the AEs (ectopic pregnancy, embedded device, and partial uterine perforation) were considered serious and all three occurred during Year 7. Five women discontinued due to

Mirena expulsion: two in Year 6 and three in Year 7. Menstrual bleeding pattern complaints as a group were the most common AEs leading to early discontinuation. Onset of menstrual bleeding complaints during the study occurred in eight women (excluding one woman with metrorrhagia beginning in Year 5), four each year and included vaginal hemorrhage, hypomenorrhea, menorrhagia, irregular menstruation, menstrual disorder, and uterine hemorrhage. Two women had unresolved outcomes, one each of weight gain and menstrual disorder.

None of the AEs leading to early discontinuation were determined to be unexpected for LNG IUS use by the Applicant or clinical review team. All of these adverse events are consistent with the safety profile for Mirena and are currently described in prescription and patient labeling.

Table 19 lists the AEs leading to discontinuation of Mirena use overall and for the last two years for comparative purposes.

Table 19. AEs Leading to Discontinuation With Onset During Yrs 6 and 7

Preferred Term **MedDRA System Organ Class** **(MedDRA Version 23.0)**	**Total Number of Women**		
	Overall **n (%)** **N=362**	**Year 6** **n (%)** **N=362**	**Year 7** **n (%)** **N=304**
Number (%) of women with at least one such AE	24 (6.6%)	11 (3.0%)	13[a] (4.3%)
Reproductive system and breast disorders	14 (3.9%)	7 (1.9%)	7 (2.3%)
Pelvic pain	3 (0.8%)	1 (0.3%)	2 (0.7%)
Vaginal haemorrhage	3 (0.8%)	1 (0.3%)	2 (0.7%)
Coital bleeding	2 (0.6%)	1 (0.3%)	1 (0.3%)
Dysmenorrhoea	1 (0.3%)	1 (0.3%)	0
Dyspareunia	1 (0.3%)	1 (0.3%)	0
Hypomenorrhoea	1 (0.3%)	1 (0.3%)	0
Menorrhagia	1 (0.3%)	1 (0.3%)	0
Menstruation irregular	1 (0.3%)	1 (0.3%)	0
Breast swelling	1 (0.3%)	0	1 (0.3%)
Breast tenderness	1 (0.3%)	0	1 (0.3%)
Menstrual disorder	1 (0.3%)	0	1 (0.3%)
Premenstrual syndrome	1 (0.3%)	0	1 (0.3%)
Uterine haemorrhage	1 (0.3%)	0	1 (0.3%)
Uterine pain	1 (0.3%)	0	1 (0.3%)
Product issues	6 (1.7%)	2 (0.6%)	4 (1.3%)
Device expulsion	5 (1.4%)	2 (0.6%)	3 (1.0%)
Embedded device	1 (0.3%)	0	1 (0.3%)
Psychiatric disorders	2 (0.6%)	1 (0.3%)	1 (0.3%)
Depression	1 (0.3%)	1 (0.3%)	0
Irritability	1 (0.3%)	0	1 (0.3%)
Infections and infestations	1 (0.3%)	1 (0.3%)	0
Vaginal infection	1 (0.3%)	1 (0.3%)	0
Injury, poisoning and procedural complications	1 (0.3%)	0	1 (0.3%)
Uterine perforation	1 (0.3%)	0	1 (0.3%)
Investigations	1 (0.3%)	1 (0.3%)	0
Weight increased	1 (0.3%)	1 (0.3%)	0
Pregnancy, puerperium and perinatal conditions	1 (0.3%)	0	1 (0.3%)
Ectopic pregnancy with contraceptive device	1 (0.3%)	0	1 (0.3%)

Source: Submission NDA 21225, SDN 1800, Study Report PH-41316, Table 10-8 p110 of 1436
[a] Thirteen (13) women had onset of AE and discontinued due to AE during Year 7. Two women discontinued due to AE during Year 7 but had onset of AE during Year 6.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities

Narratives for the 15 women experiencing AEs leading to discontinuation during Year 7 of Mirena use are summarized in Table 20. Narratives for women experiencing AEs leading to discontinuation regardless of severity during Year 6 are summarized in the previous review (Food and Drug Administration 2020).

Table 20. Discontinuations Due to AE Occurring During Year 7 (Narratives)

Subject ID Number Age (Years) Start Relative to Day 1 Year 6	AE Preferred Term	Narrative/Case Report Form
(b) (6) 33 y/o Day 246	Vaginal hemorrhage	Presented with vaginal spotting on (b) (6). Experienced vaginal cramping from (b) (6) and (b) (6) to (b) (6). Mirena removed (b) (6) due to vaginal spotting. The event resolved (b) (6).
(b) (6) 31 y/o Day not calculated	Weight increased	Presented with weight gain and worsening hypothyroidism in (b) (6). Weight increased from 208 to 227 pounds from (b) (6) to (b) (6). Mirena removed (b) (6) due to weight gain. AE not resolved at last report.
(b) (6) 26 y/o Day 387	Breast tenderness Pelvic Pain Vaginal hemorrhage	Presented with vaginal bleeding, pelvic cramping, and bilateral breast tenderness on (b) (6). Mirena removed (b) (6) due to the AEs. AEs resolved (b) (6).
(b) (6) 29 y/o Day 545	Device expulsion	On (b) (6) presented with device expulsion. On IUS was not located on TVUS. On (b) (6), IUS was not located on TVUS or x-ray and UPT was negative. IUS was deemed to be expelled on (b) (6). Previous TVUS (b) (6) performed due to strings not visualized with imaging showing IUS in situ. Event of device expulsion resolved with sequelae (pregnancy) on (b) (6). Date of conception based on menstrual period was (b) (6) 27 days after Mirena expulsion was recognized.
(b) (6) 30 y/o Day not calculated	Irritability	Presented with premenstrual syndrome mood/irritability in (b) (6) (6 years and 2 months after Mirena insertion). Mirena removed (b) (6). AE resolved (b) (6)
(b) (6) 28 y/o Day 500	Embedment device	SAE – see Table 18 above.
(b) (6) 28 y/o Day not calculated	Vaginal hemorrhage	Presented with vaginal bleeding in (b) (6) (6 years, 9 months after Mirena insertion). Mirena removed (b) (6) due to vaginal bleeding. AE resolved in (b) (6).
(b) (6) 27 y/o Day 422	Device expulsion Coital bleeding Pelvic pain	Presented with coital bleeding and pelvic pain on (b) (6). On (b) (6) a TVUS showed a partial device expulsion. Mirena was removed the same day. The AEs resolved (b) (6).
(b) (6) 26 y/o Day 545	Uterine perforation (partial)	SAE – see Table 18 above.

Subject ID Number Age (Years) Start Relative to Day 1 Year 6	AE Preferred Term	Narrative/Case Report Form
(b) (6) 32 y/o Day 655	Breast swelling	Presented with breast swelling on (b) (6) Mirena removed (b) (6). AE resolved (b) (6).
(b) (6) 33 y/o Day not calculated	Premenstrual syndrome Uterine bleeding	Presented with premenstrual syndrome and uterine bleeding in (b) (6) (6 years and 11 months after Mirena insertion). Mirena was removed (b) (6). Outcome of AEs unknown.
(b) (6) 25 y/o Day 521	Menstrual disorder	Presented with abnormal menstrual bleeding on (b) (6). Mirena removed (b) (6). AE not resolved at last recorded outcome.
(b) (6) 27 y/o Day 584	Ectopic pregnancy with contraceptive device	SAE – see Table 18 above
(b) (6) 33 y/o Day 557	Device expulsion	Presented with partially expelled IUS when TVUS performed. Mirena removed (b) (6). AE resolved on (b) (6).
(b) (6) 32 y/o Day 478	Uterine pain	Presented with uterine pain on (b) (6). Mirena removed (b) (6), due to pain. AE resolved (b) (6)

Source: Submission NDA 21225, SDN 1800, Study Report PH-41316, Table 10-9 p 112/1436 and Narratives p1189 of 1436
Abbreviations: AE, adverse event; IUS, intrauterine system; SAE, serious adverse event; TVUS, transvaginal ultrasound; UPT, urine pregnancy test; y/o, years old

Significant Adverse Events

Adverse events of special interest (AESI) associated with LNG IUSs that are considered clinically significant include uterine perforation, IUS expulsion, pelvic infections including pelvic inflammatory disease (PID) and endometritis, sepsis, and ovarian cysts. Ectopic pregnancy, although an efficacy failure, is also considered an AESI for IUSs. The AESIs and number of AESIs occurring during the study do not raise a concern for any AESI increasing in frequency during extended use of Mirena.

The number of AESIs experienced during Years 6 and 7 occurred less frequently than in the pivotal clinical trials of Mirena use up to six years and are presented in Table 21.

Table 21. Adverse Events of Special Interest During Yrs 6 and 7

AE	Overall n (%) N=362	Year 6 n (%) N=362	Year 7 n (%) N=304
Uterine perforation[a]	2 (0.6)	0	2 (0.7)
Pelvic infections including PID and endometritis	0	0	0
IUS expulsion	5 (1.4)	2 (0.6)	3 (1.0)
Ovarian cysts (excluding benign ovarian teratoma)	5 (1.9)	3 (0.8)	2 (0.7)
Ectopic pregnancy	1 (0.3)	0	1 (0.3)

Source: Submission NDA 21225, SDN 1800, Study Report PH-41316, Sections 10.4 p113, 10.6 p117 of 1436, and 16.2.7 Adverse Event Listings
[a]including embedment, considered partial uterine perforation
Abbreviations: AE, adverse event; IUS, intrauterine system; PID, pelvic inflammatory disease

Eight women discontinued Mirena use during Years 6 and 7 due to an AESI (2 partial uterine perforations/embedment, 5 IUS expulsions, 1 ectopic pregnancy) and the narratives are presented in Table 18 (SAE) and Table 20 (AE leading to discontinuation). Five women were reported to experience ovarian cysts. None of these cysts required treatment or led to subject discontinuation.

There was one suspected case of PID: A 35-year-old (Subj ID # (b) (6)) experienced the non-serious adverse event of salpingo-oophoritis on (b) (6) She had complaints of lower abdominal pain. At the clinic visit, no fever, no vaginal discharge, and some tenderness on pelvic examination were noted. On (b) (6), Rocephin injection was administered and she was started on doxycycline for two weeks. On (b) (6) at her Visit 5 contact, she expressed her desire for permanent sterilization. Doxycycline was continued until (b) (6) when she underwent laparoscopic bilateral salpingectomy and Mirena was removed. At the time of laparoscopy, there was no indication of any upper genital tract infection. Based on the criteria for a diagnosis of PID in the protocol, this event does not represent a confirmed case of PID for the purposes of calculating a rate.

Treatment Emergent Adverse Events (TEAE)

No unexpected AEs occurred in the sixth and seventh year of Mirena use.

A total of 230 of the 362 women (63.5%) reported at least one AE occurring on or after Day 1 of Year 6. Infections and infestations and Reproductive system and breast disorders made up the majority of the system-organ class AEs. The frequencies of AEs were similar in Years 6 and 7.

Table 22. AEs Occurring in ≥2% of Women by MedDRA System Organ Class

MedDRA System Organ Class MedDRA Version 23.0	Overall n (%) N=362	Year 6 n (%) N=362	Year 7 n (%) N=304
Number (%) of women with at least one such adverse event	230 (63.5%)	170 (47.0%)	142 (46.7%)
Infections and infestations	117 (32.3%)	76 (21.0%)	61 (20.1%)
Reproductive system and breast disorders	76 (21.0%)	42 (11.6%)	39 (12.8%)
Psychiatric disorders	47 (13.0%)	32 (8.8%)	16 (5.3%)
Investigations	41 (11.3%)	26 (7.2%)	16 (5.3%)
Gastrointestinal disorders	27 (7.5%)	15 (4.1%)	13 (4.3%)
Musculoskeletal and connective tissue disorders	25 (6.9%)	14 (3.9%)	12 (3.9%)
Skin and subcutaneous tissue disorders	24 (6.6%)	12 (3.3%)	12 (3.9%)
Injury, poisoning and procedural complications	23 (6.4%)	12 (3.3%)	12 (3.9%)
Nervous system disorders	16 (4.4%)	12 (3.3%)	4 (1.3%)
Respiratory, thoracic and mediastinal disorders	14 (3.9%)	7 (1.9%)	8 (2.6%)
General disorders and administration site conditions	11 (3.0%)	8 (2.2%)	3 (1.0%)
Surgical and medical procedures	11 (3.0%)	5 (1.4%)	6 (2.0%)
Immune system disorders	9 (2.5%)	7 (1.9%)	4 (1.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (2.5%)	5 (1.4%)	3 (1.0%)

Source: Submission NDA 21225, SDN 1800, Study Report PH-41316, Table 10-2, p101 of 1436

AEs that were reported as being severe in intensity were experienced by 13 women (3.6%). During Year 7, all severe AEs occurring in four women were also SAEs (uterine perforation,

obesity, embedded device, suicide attempt /suicidal ideation/ depression). Nine women experienced severe AEs during Year 6 (Food and Drug Administration 2020). The SAEs occurring during Year 7 are described in Table 18 (SAE).

AEs considered safety concerns and occurring during Years 6 and 7 are tabulated in Table 23. The frequencies of AEs were similar for Years 6 and 7 and overall, occurred less frequently than adverse drug reactions (ADR) occurring during the pivotal clinical trials as presented in the label. Of the reactions that were identified, only anxiety reaction and weight gain occurred in over 5% of women in the MET and are not included in the current Mirena label.

Weight gain is considered an AE in other progestin-only contraceptives, including LNG IUS and should be added in the label as an AE experienced by women during the MET. Because over 23% of women in the MET reported a history of anxiety, anxiety reaction was not included in the label as an AE as it is unclear that this event is related to Mirena use based on the clinical trial data.

Table 23. Frequency of Labeled AE Groupings Occurring in Women During Years 6 and 7, Cumulative

		Number of Subjects n (%)
System Organ Class	**MedDRA Labeling Grouping (MLG)**	**N=362**
Infections and infestations	Vulvovaginal infections	36 (9.9)[a]
Reproductive system and breast disorders	Female genital tract bleeding	19 (5.2)
	Increased schedule uterine bleeding	9 (2.5)
	Breast pain	9 (2.5)
	Dysmenorrhea	6 (1.7)
	Unscheduled uterine bleeding	7 (1.9)
	Genital discharge	4 (1.1)
	Benign ovarian cyst and associated complications	4 (1.1)
	Decreased uterine bleeding	1 (0.3)
	Amenorrhea	2 (0.6)
Gastrointestinal disorders	Gastrointestinal and abdominal/pelvic pain	21 (5.8)[a]
Nervous system disorders	Headache/migraine	9 (2.5)[a]
Musculoskeletal and connective tissue disorders	Back pain	6 (1.7)
Skin and subcutaneous tissue disorders	Acne	9 (2.5)
Metabolism	Weight increase	23 (6.4)
Psychiatric disorders	Anxiety reaction	19 (5.2)
	Depression/depressive mood	18 (5)[a]

Source: Submission NDA 21225, SDN 1800, Study Report PH-41316, Year 7 Analysis AE for Labeling, Tables 1.1/1 p3 of 51 and 1.1/4 p41 of 51.
MLG: MedDRA labeling groupings are the same, or similar (in different MedDRA version) for MET and Adverse drug reaction presented in the Mirena FDA-approved label. See Bayer Response to FDA IR submitted April 1, 2021, SDN 1866.
[a] Table 1.1/4; remaining data from Table 1.1/1
Abbreviation: AE, adverse event

Laboratory Findings

Laboratory evaluations performed included serum clinical laboratories (chemistry, hematology), urinalysis, cervical smear (PAP) test, and test for Chlamydia during the trial. No laboratory evaluations during Years 6 and 7 resulted in early discontinuation of Mirena.

Clinical Laboratory Evaluations

Most of the laboratory parameters were within normal range. Eleven women (3.0%) had elevated laboratory evaluation listed as an AE. Of these eleven women, five had elevated liver enzymes, none with values over 3 times normal range. The remaining AEs were increased creatinine, elevated hemoglobin A1C, triglyceride elevated, urine leukocytes, and abnormal eosinophils. Within the safety population, the only laboratory parameter value above the normal range occurring in more than 10% of women was triglycerides (10.6%). None of the abnormal triglyceride values led to participant discontinuation.

Cervical Smear Test

A normal or clinically insignificant cervical smear (PAP) was an inclusion requirement. Another cervical smear was obtained from 70 of 81 women who discontinued prematurely. Four of these 70 women (5.7%) had abnormal smears, none of which were high grade abnormalities. The women were referred to their gynecologists for follow up.

Test for Chlamydia

A negative Chlamydia test was an inclusion requirement. During screening, six women had positive Chlamydia results with resolution of the infections without requiring Mirena removal. All six women tested negative for gonorrhea. During Year 6, two women experienced Chlamydia infections as an AE with the outcome of resolution.

Other Safety Assessments

Additional safety assessments during the MET trial included vital signs, body weight and calculated BMI, and findings on physical examinations. All gynecological findings found after screening were recorded as an AE**.**

Vital Signs

Overall, mean changes in systolic and diastolic blood pressure were below 3 mm Hg. The mean change in heart rate was below 3 beats per minute. Five women had elevated blood pressure/hypertension listed as an AE, none discontinued the study due to the AE. However, one of the women (Subj ID # (b) (6)) was discontinued from the study due to physician decision based on her continuing noncompliance with hypertension medications. At the time of her End of Treatment visit, she had a blood pressure of 162/110, the highest blood pressure recorded during the study.

Body Weight/BMI

Overall, the mean change from baseline to month 24 in body weight was approximately 2 kg and the mean change in BMI was 0.8 kg/m^2. However, 28 women (7.7%) experienced weight gain of 10 kg or more: 13 women during the first 12 months of the study, an additional 13 women during the second 12 months, one woman at the End of Treatment, and one woman

during the first 18 months of the study. Weight gain was considered an AE in 23 women (6.4%). One woman (Subj ID # (b) (6)) discontinued the study due to weight gain.

Weight loss of 10 kg or more was experienced by 13 women (3.6%): 10 women in the first 12 months and 3 women in the second 12 months of the study. Weight loss was considered an AE in 2 women (0.6%).

Electrocardiograms (ECGs)

Not applicable

QT

Not applicable

Immunogenicity

No events suggestive of drug allergy or angioedema occurred during Years 6 and 7 of Mirena use.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Uterine Bleeding Profile

The uterine bleeding profile of Years 6 and 7 of Mirena use was reported as a safety endpoint to inform Section 6 of the Mirena label. Uterine bleeding data were recorded daily in eDiaries, analyzed, and reported for 28-day and 90-day reference periods (see Study Endpoints and Statistical Analysis Plan in Section 8.1.1). Women reported bleeding as none, spotting (use of panty liner only), or bleeding (use of sanitary protection). Women reported intensity of bleeding (light, normal, heavy); however, for uterine bleeding pattern analysis, all bleeding intensities were collapsed into one "bleeding" category.

Nine women (2.5%) discontinued Mirena use due to bleeding complaints; four during Year 6 (one onset before year 6) and five during Year 7 (one onset in Year 6). The bleeding complaints were three vaginal hemorrhage (one described as spotting), one uterine bleeding, one menorrhagia, one metrorrhagia, one abnormal menstrual bleeding, one irregular menses, and one hypomenorrhea. None of these nine women were from the HMB subgroup.

The proportion of women experiencing amenorrhea in the first four 90-day reference periods (Year 6)[2] were 18.4 to 24.2% and in the second four 90-day reference periods (Year 7) were 22.9 to 27.8%. Other bleeding patterns were stable throughout the eight 90-day reference periods. At the last recorded 90-day reference period, the proportion of women experiencing

[2] Within each 90-day reference period, up to 5 nonconsecutive days of missing bleeding data were replaced using the maximal bleeding intensity of the day before or the day after the missing day. If bleeding data was missing in 3 consecutive days or more than 5 days within the 90-day period, the reference period was considered invalid.

bleeding patterns were: infrequent bleeding 26.1%, frequent bleeding 7.8%, irregular bleeding 12.2%, prolonged bleeding 1.7%.

The proportion of women with bleeding and spotting and the number of days of bleeding and spotting by 28-day reference periods[3] remained stable through Years 6 and 7. Overall, approximately 55 to 65% of women experienced bleeding and spotting during a 28-day treatment cycle for a mean of 2.5 to 3 days, and approximately 25 to 30% of women experienced bleeding for a mean of 1 day or less during each 28-day period. This bleeding data is consistent with LNG IUS use. Results from the analyses through year 7 on bleeding and spotting were expected outcomes and updated data were included in the prescription labeling.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The uterine bleeding profile with extended Mirena use was determined from daily eDiary data entered by women throughout the study. Findings are presented in Section 8.2.5.1.

8.2.7. Safety Analyses by Demographic Subgroups

Overall, safety analyses by demographic subgroups for Years 6 and 7 did not show clinically significant differences between subgroups. Tabulation of AEs by subgroups was provided and shown in Table 24 below:

Table 24. Safety Analyses by Demographic Subgroups

Demographic Parameter	Frequency of AE by Subgroup
Age in years at baseline	18-25: 61.0% 26-35: 63.9%
BMI	<30 kg/m^2: 62.5% ≥30 kg/m^2: 65.8%
Parity	Nulliparous: 67.8% Parous: 59.7%
Race	White: 63.0% Black: 70.6%
Ethnicity	Hispanic/Latina: 43.9% Not Hispanic/Latina: 65.8%

Source: Submission NDA 21225, SDN 1800, Study Report PH-41316, Year 7 Analysis AE in Subgroups Table 1.1/3 p40 of 119, Table 1.1/5 p55 of 119, Table 1.1/6 p69 of 119, Table 1.1/7 p83 of 119, Table 1.1/8 p102 of 119
Abbreviations: AE, adverse event; BMI, body mass index

Some differences in frequencies of AEs between BMI categories were identified and are shown in Table 25. Women with a BMI of ≥30 kg/m^2 had an increased frequency of weight gain compared to women with a BMI of <30 kg/m^2 (8.8% versus 5.2%). Conversely, women in the lower BMI subgroup had a higher frequency of Psychiatric disorders and Reproductive system and breast disorders. No conclusions can be made regarding these differences due to the small

[3] Within each 28-day reference period, up to 2 days of missing bleeding data were replaced using the maximal bleeding intensity of the day before or after the missing day. If bleeding data was missing in more than 2 days, the reference period was considered invalid. Episodes of bleeding or spotting were defined by at least 2 bleeding-free days before and after the episode.

number of women experiencing individual AEs and lack of baseline medical and gynecological history.

Device expulsion occurred in 4 women: 2 women in each BMI subgroup.

Table 25. Selected AEs Reported Occurring in Women by Body Mass Index

SOC	<30 kg/m^2 n (%) N=248	≥30 kg/m^2 n (%) N=114
Psychiatric disorders	37 (14.9)	10 (8.8)
Depression	13 (5.2)	4 (3.5)
Anxiety	12 (4.8)	2 (1.8)
Reproductive system and breast disorders	58 (23.4)	18 (15.8)
Bleeding (includes amenorrhea)[a]	31 (12.5)	8 (7.0)
Gynecologic pain[b]	19 (7.7)	4 (3.5)

Source: Submission NDA 21225, SDN 1800, Study Report Body Chapter, Year 7 Analysis AE in Subgroups Table 1.1/5, p55 of 119.
[a] includes menorrhagia, vaginal hemorrhage, metrorrhagia, coital bleeding, uterine hemorrhage, amenorrhea, hypomenorrhea, menstruation irregular, polymenorrhagia, cervix hemorrhage uterine
[b] includes pelvic pain, dyspareunia, dysmenorrhea, adnexa uteri pain, perineal pain, uterine pain
Abbreviations: AE, adverse event; SOC, system organ class

AE frequencies occurring in nulliparous versus parous women were similar except all four expulsions occurred in parous women (all four had Mirena inserted within two months after last birth or abortion).

Clinically meaningful comparisons between subgroups in age, race, and ethnicity are not possible due to the small number of women in many of the subgroups (see Table 10 Demographics).

8.2.8. Specific Safety Studies/Clinical Trials

None.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No human carcinogenicity studies were necessary to extend use of Mirena.

Human Reproduction and Pregnancy

Pregnancy outcomes with Mirena use are followed and information was updated in labeling. No additional nonclinical or clinical studies beyond the results of the MET were necessary to extend Mirena use through year 7.

Pediatrics and Assessment of Effects on Growth

No pediatric studies were conducted. A pediatric study plan (PSP) was submitted and reviewed to comply with the Pediatric Research Equity Act (PREA), see Section 10. The PSP was determined to be acceptable by Pediatric Review Committee (PeRC) and the Division.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

To support the safety of Mirena use beyond five years, the Division requested that the Applicant compile and submit evaluations of AEs in postmarketing reports with documentation of over five years of continuous Mirena use. The Applicant was to provide case reports and subject narratives for pregnancies, deaths, SAEs, perforations, expulsions, and infections. A "Patients Who Used a Single Mirena for >5 Years: Summary of Postmarketing Reports" (Initial report) was prepared by the Applicant and submitted on October 21, 2019 within S-040 (Year 6) and included reports between 2013 and May 8, 2019. The document was previously reviewed in the Year 6 Unireview (Food and Drug Administration 2020). A supplementary document, "Patients Who Used a Single Mirena for >5 Years: Summary of Postmarketing Reports. Supplement with Reports Received Between May 9, 2019 and May 8, 2020" (Supplement report) was submitted by the Applicant on October 13, 2021 within S-042 (Year 7) and reviewed below.

In preparing the Initial and Supplement reports, the Applicant's global pharmacovigilance database was searched for cases reports based on AE terms suggestive of prolonged use. The Initial report evaluated 2,130 case reports for pregnancies, AEs which included deaths, SAEs, infections, expulsions, and perforations (perforations tabulated separately from other AEs). Narratives were included for pregnancies, deaths, SAEs, IUS expulsions, and uterine perforations (Food and Drug Administration 2020). The Supplement report has a total of 344 validated new cases flagged as use beyond labeled duration. Of the 344 cases, 224 cases (65.1%) also described an AE, including pregnancy. Eight cases referenced the COVID-19 lockdown as a reason for delayed removal. Two of these 8 cases had a non-serious AE and are included in the 224 cases described below. The reporting rate of use beyond labeled duration was 0.09 per 1000 units sold (2.3 per 100,000 WY of estimated exposure) and is the same as the reporting rate calculated for the Initial report.

Overall, the 224 cases flagged as use beyond labeled duration with a pregnancy, AE or device issue, or perforation comprised:

- Three cases of pregnancy, 188 cases describing an AE/device issue, and 33 cases of uterine perforation including embedment.
- The majority (88.4%) of the cases came from spontaneous reports.
- Duration of use from five to seven years made up approximately 60% of the cases. The duration for the remaining 40% of cases were >8 years and >5 years, not otherwise specified.

Pregnancy

The three cases of pregnancy not associated with expulsion occurred at >5, 6, and 6.5 years with outcomes of one missed/spontaneous abortion, one ectopic pregnancy, and one ongoing pregnancy at the time of report. The outcomes are consistent with labeled outcomes and do not indicate new safety signals not already in current prescription and patient labeling.

AEs

The 188 cases of an AE/device issue exclude uterine perforation (an AE) and pregnancy. The 188 AE/device issue cases were received from approximately one third each the US, Europe, and other countries.

The 188 AE/device issue cases include:

- 1 case with fatal outcome
- 12 cases with infection
- 64 cases with SAE (excluding 8 cases with infection and one fatal outcome)
- 111 cases with other AEs which included 13 cases of expulsion

Fatal Outcome

A 46-year-old woman (case (b) (6) died from an unknown cause, approximately 7 weeks after replacement of the first Mirena (used for approximately 6 years) by a second one. Medical history and comorbidities were not reported; however, the patient was reportedly taking several cardiovascular drugs including digoxin, dofetilide, metoprolol, torasemide, selexipag, sildenafil, montelukast, and warfarin, suggesting the presence of significant cardiopulmonary comorbidity such as pulmonary arterial hypertension and heart failure. The reporter provided no causality assessment for the patient's death. Based on the information provided in the adverse report, an association between prolonged Mirena use and death cannot be made.

Infections

The twelve reports of infections include four reports of a serious infection, four reports of an SAE with a nonserious infection, and four reports of nonserious infections.

The four cases of serious infections are one each of: salpingo-oophoritis, tubo-ovarian abscess, Lyme disease, and device related infection (cultured IUS positive for MRSA; no information on clinical presentation of 34-year-old patient). The four cases of an SAE are three cases of hemorrhage and one case of device breakage with removal with nonserious infections of fungal infections and urinary tract infections. The four nonserious infections were two reports of candidiasis and single reports of urinary tract infection and bacterial vaginosis.

The infections reported are consistent with infections experienced by postmenarchal women. Information on the risks of PID with Mirena use are well known to clinicians and prominent in prescription and patient labeling.

SAEs

There were 73 SAEs: one death, 8 SAES with infection, 64 other SAEs. These 73 cases comprise approximately 40% of the 188 cases with AEs.

SAEs reported in more than one case are presented in Table 26. SAEs occurring in >5 to 6 years make up 46.9% of SAEs reported. The most common SAEs reported are device breakage, device dislocation, and genital hemorrhage. Due to the small number of cases in each PT, trends for increased frequency of SAEs with increasing duration of use cannot be determined. The Initial Report, with 552 SAEs, did not show any trends by duration of use for the three most common SAEs reported.

Table 26. Most Commonly Reported SAEs By Duration of Use >5 Years (Cut Off ≥2%)[1,2]

SAE (MedDRA PT)	Duration of use													
	>5 to 5.25 yrs		>5.25 to 6 yrs		>6 to 7 yrs		>7 to 8 yrs		>8 yrs		>5 yrs NOS[3]		Total	
	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases
Device breakage	3	37.5%	6	27.3%	2	12.5%	1	50.0%	6	40.0%	--	--	18	28.1%
Device dislocation	2	25.0%	5	22.7%	4	25.0%	1	50.0%	2	13.3%	1	100.0%	15	23.4%
Genital haemorrhage	3	37.5%	4	18.2%	3	18.8%	1	50.0%	2	13.3%	--	--	13	20.3%
Device issue	--	--	1	4.5%	--	--	--	--	1	6.7%	--	--	2	3.1%
Vomiting	--	--	--	--	1	6.3%	--	--	1	6.7%	--	--	2	3.1%
(...)														
Total	**8**	**100.0%**	**22**	**100.0%**	**16**	**100.0%**	**2**	**100.0%**	**15**	**100.0%**	**1**	**100.0%**	**64**	**100.0%**

[1] Excluding terms coding the prolonged use as such.
[2] Sums may exceed total number of cases / 100% because more than one adverse event/device issue might have been reported in a case.
[3] Cases reporting use for >5 years but with insufficient information to allow further classification of duration.

Source: Submission NDA 21225, SDN 1900, Bayer Response to 07 July 2021 FDA Clinical IR, Table 3-12 (Correction), p3 of 7.

Review of narratives for the SAE reports provides some insight on device issues encountered.

- Device breakage often occurs with complication of device removal; of the 18 device breakages, 16 also involved complication of device removal
- Device breakage includes retrieval string detaching from the IUS
- Device breakage with complication of device removal includes events of the hormone reservoir sliding off the T-body and sliding over the arms of the IUS giving the appearance of missing/broken off arms.
- Device dislocation includes retrieval string not found and IUS abnormally positioned in the uterus

Labeling changes to inform healthcare providers (HCP) of increased device breakage with complication of device removal should be implemented. In the current label, device breakage is listed in Section 6.2 Postmarketing Experience. In Section 2.4 Removal of Mirena, the HCP is directed to apply gentle traction on the threads and after removal, examine the system to ensure that it is intact.

AE/Device Issues

Many of the AE/device issues reported appear to be related to device issues. AE/device issues occurring in ≥3% of the reported cases are shown in Table 27.

Table 27. Use >5 Years: Most Commonly Reported AE/Device Issues Occurring ≥3%[1,2]

Adverse event (MedDRA PT)	Duration of use													
	>5 to 5.25 yrs		>5.25 to 6 yrs		>6 to 7 yrs		>7 to 8 yrs		>8 yrs		>5 yrs NOS[3]		Total	
	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases
Complication of device removal	4	19.0%	15	23.1%	5	12.8%	3	17.6%	13	37.1%	2	18.2%	42	22.3%
Amenorrhoea	4	19.0%	8	12.3%	2	5.1%	6	35.3%	7	20.0%	--	--	27	14.4%
Device breakage	3	14.3%	8	12.3%	3	7.7%	2	11.8%	6	17.1%	--	--	22	11.7%
Device use issue	3	14.3%	5	7.7%	4	10.3%	1	5.9%	3	8.6%	2	18.2%	18	9.6%
Device physical property issue	--	--	9	13.8%	3	7.7%	2	11.8%	3	8.6%	--	--	17	9.0%
Device dislocation	2	9.5%	6	9.2%	4	10.3%	1	5.9%	2	5.7%	1	9.1%	16	8.5%
Genital haemorrhage	4	19.0%	5	7.7%	3	7.7%	2	11.8%	2	5.7%	--	--	16	8.5%
Off label use of device	1	4.8%	6	9.2%	2	5.1%	1	5.9%	5	14.3%	--	--	15	8.0%
Device difficult to use	2	9.5%	6	9.2%	3	7.7%	1	5.9%	1	2.9%	--	--	13	6.9%
Device expulsion	1	4.8%	5	7.7%	2	5.1%	--	--	5	14.3%	--	--	13	6.9%
Procedural pain	2	9.5%	2	3.1%	4	10.3%	--	--	3	8.6%	1	9.1%	12	6.4%
Complication of device insertion	1	4.8%	4	6.2%	4	10.3%	2	11.8%	--	--	1	9.1%	12	6.4%
Vaginal haemorrhage	--	--	3	4.6%	2	5.1%	1	5.9%	3	8.6%	1	9.1%	10	5.3%
Abdominal pain lower	3	14.3%	2	3.1%	1	2.6%	--	--	1	2.9%	1	9.1%	8	4.3%
Vaginal discharge	2	9.5%	2	3.1%	2	5.1%	1	5.9%	1	2.9%	--	--	8	4.3%
Depression	--	--	2	3.1%	1	2.6%	--	--	3	8.6%	--	--	6	3.2%
Device issue	--	--	3	4.6%	--	--	--	--	2	5.7%	1	9.1%	6	3.2%
Fatigue	--	--	1	1.5%	2	5.1%	1	5.9%	1	2.9%	1	9.1%	6	3.2%
(...)														
Total	21	100.0%	65	100.0%	39	100.0%	17	100.0%	35	100.0%	11	100.0%	188	100.0%

[1] Excluding terms coding the prolonged use as such.
[2] Sums may exceed total number of cases / 100% because more than one adverse event/device issue might have been reported in a case.
[3] Cases reporting use for >5 years but with insufficient information to allow further classification of duration.

Source: Submission NDA 21225, SDN 1800, Patient Who Used a Single Mirena for >5 Years: Summary of Postmarketing Reports, Supplement with Reports Received Between May 9, 2019 and May 8, 2020, dated July 31, 2020, Table 3-10, p15 of 108.

There do not appear to be increased frequencies of device issues comparing up to 6, 7, and 8 years of use, noting the small number of cases in each PT. For reports of device use >8 years, complication of device removal, device breakage, and device expulsion were reported more frequently (Table 27). Device breakage and device expulsion are described in the Mirena label in Sections 6.2 Postmarketing Experience and 5.6 Expulsion, respectively. Breakage and complication of device removal may be related to how the device was inserted (e.g., embedded into the myometrium) and how the device is removed (e.g., with forceps). Similarly, device dislocation and device issues may be related to operator placement of the device. It is difficult to determine if these events are occurring primarily due to extended Mirena use or due to other conditions based on postmarketing AE reports.

Bleeding AEs listed include amenorrhea and genital and vaginal hemorrhage. Amenorrhea is common with LNG IUSs and may be considered either a benefit or an adverse side effect by different users. Both genital and vaginal hemorrhage include spotting and “vaginal bleeding like discharge” and are common side effects of LNG IUSs. Bleeding patterns are described in Sections 5.8 Bleeding Pattern Alterations and 6.1 Clinical Trials Experience of the label and also included in patient labeling.

Uterine Perforation

Of the 224 cases flagged for use beyond labeled duration, there were 33 cases of uterine perforation. These 33 uterine perforation cases make up 3.4% of all postmarketing reports of uterine perforation in Mirena users received during the reporting period. Twenty-eight of the 33 cases were medically confirmed. All reports were spontaneous.

The AEs categorized as a uterine perforation were: 21 embedded device, 7 extrauterine/ intraabdominal location, and 5 uterine perforation. Reports of embedded device increased in frequency for device use >7 years, although this trend is based on small numbers of events (Table 34). Uterine perforation reports did not show a trend with duration of use. Extrauterine/intraabdominal location reports were not reported by years of use. The most commonly reported AE/device issues other than uterine perforation in the 33 cases are complication of device removal (17 cases), device breakage (14 cases) and device difficult to use (7 cases).

Uterine perforation is of concern as can cause serious infection and/or difficult device removal. After review of the safety profile and clinical trial data, no increase was reported with continued use through year 7. Based on current clinical assessment of the data, the risk of uterine perforation is adequately described in Section 5.5 Perforation of the Mirena label.

Postmarketing Conclusion

The Applicant presented the frequencies of AEs, including pregnancy that were reported in cases of Mirena use beyond labeled duration (Table 34). In the Supplement report of 224 cases, there does not appear to be an increase of AEs with extended use up to 6, 7, and 8 years. For use >8 years, AEs of Complication of device removal, Device breakage, Embedded device, and Device expulsion occurred proportionally more frequently. Because the numbers of cases for each PT are small, it is difficult to make any conclusions.

However, review of the Initial report with 2,130 cases over approximately 20 years' timeframe does not show clinically large increases in AE frequencies, rather small increases in categories including: Device dislocation, Device breakage, and Drug ineffective with duration of use >8 years (Table 28). Because the frequencies are based on postmarketing reports, these small increases in proportionality may not have clinical relevance. Additionally, the frequencies of these AEs for Mirena use less than 5 years is not presented for comparison.

Table 28. Summary Tabulation From Initial Report

Summary tabulation: Use >5 years – All cases included in the analysis (N=2,130), by duration of use[1,2]

Adverse event (MedDRA PT)	Duration of use													
	>5 to 5.25 yrs		>5.25 to 6 yrs		>6 to 7 yrs		>7 to 8 yrs		>8 yrs		>5 yrs NOS[3]		Total	
	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases
Complication of device removal	62	21.99%	138	20.23%	68	17.22%	35	18.04%	54	18.37%	38	13.43%	395	18.54%
Amenorrhoea	40	14.18%	94	13.78%	65	16.46%	31	15.98%	53	18.03%	54	19.08%	337	15.82%
Device issue	64	22.70%	119	17.45%	51	12.91%	30	15.46%	33	11.22%	27	9.54%	324	15.21%
Uterine perforation	51	18.09%	112	16.42%	44	11.14%	30	15.46%	36	12.24%	6	2.12%	279	13.10%
Injury	67	23.76%	121	17.74%	42	10.63%	24	12.37%	15	5.10%	5	1.77%	274	12.86%
Device dislocation	38	13.48%	71	10.41%	44	11.14%	26	13.40%	42	14.29%	33	11.66%	254	11.92%
Device breakage	33	11.70%	84	12.32%	38	9.62%	21	10.82%	44	14.97%	19	6.71%	239	11.22%
Embedded device	38	13.48%	87	12.76%	49	12.41%	25	12.89%	24	8.16%	16	5.65%	239	11.22%
Pain	50	17.73%	93	13.64%	31	7.85%	21	10.82%	17	5.78%	7	2.47%	219	10.28%
Genital haemorrhage	22	7.80%	71	10.41%	33	8.35%	14	7.22%	19	6.46%	16	5.65%	175	8.22%
Emotional distress	42	14.89%	70	10.26%	24	6.08%	18	9.28%	7	2.38%	2	0.71%	163	7.65%
Procedural pain	25	8.87%	52	7.62%	30	7.59%	17	8.76%	18	6.12%	17	6.01%	159	7.46%
Abdominal pain lower	20	7.09%	54	7.92%	30	7.59%	14	7.22%	13	4.42%	15	5.30%	146	6.85%
Anxiety	28	9.93%	59	8.65%	23	5.82%	14	7.22%	13	4.42%	7	2.47%	144	6.76%
Abdominal pain	25	8.87%	44	6.45%	23	5.82%	21	10.82%	16	5.44%	8	2.83%	137	6.43%
Complication of device insertion	11	3.90%	48	7.04%	32	8.10%	14	7.22%	15	5.10%	13	4.59%	133	6.24%
Pregnancy with contraceptive device	18	6.38%	44	6.45%	23	5.82%	14	7.22%	21	7.14%	8	2.83%	128	6.01%
Drug ineffective	18	6.38%	35	5.13%	21	5.32%	15	7.73%	24	8.16%	12	4.24%	125	5.87%
Device use issue	10	3.55%	44	6.45%	21	5.32%	11	5.67%	20	6.80%	11	3.89%	117	5.49%
Depression	19	6.74%	40	5.87%	19	4.81%	14	7.22%	15	5.10%	7	2.47%	114	5.35%
Vaginal haemorrhage	18	6.38%	44	6.45%	22	5.57%	4	2.06%	7	2.38%	14	4.95%	109	5.12%

Source: Submission NDA 21225, SDN 1670, Patient Who Used a Single Mirena for >5 Years: Summary of Postmarketing Reports dated 21 August 2019, page31 of 1599.

Expectations on Safety in the Postmarket Setting

Based on postmarketing FAERS reports, Mirena use up to 7 years has an acceptable safety profile for users. Review of postmarketing reports has not shown an increasing trend for any single AE (other than amenorrhea) during Mirena use from >5 years to 7 years. Narratives from the postmarketing reports suggest device breakage can occur with difficult device removals. This information will be incorporated into the Mirena label.

8.2.11. Integrated Assessment of Safety

The safety of Mirena use for contraception up to 7 years is based on the 2-year findings of the MET (a phase 3 multicentered study in the United States to evaluate the contraceptive efficacy and safety of Mirena during extended use for up to 8 years) and supportive safety evidence from a Summary of Postmarketing Reports on patients who used a single Mirena for greater than five years. The MET safety database found no new or unexpected safety trends in adverse events or laboratory findings. The Summary of Postmarketing Reports, both Initial and Supplement, show no trends of increased frequency of AEs with extended Mirena use up to 7 years.

The MET clinical safety database is comprised of 362 US women aged 18 to 35 years who provided 5,524 28-day cycles (577 WY) of Mirena exposure. Almost half of the woman were nulliparous and a third were obese. A total of 240 women completed 24 months (Years 6 and 7) of treatment. Because T-shaped LNG IUSs are not a new contraceptives and have a known

safety profile, the safety database, despite having less than 10,000 evaluable cycles, is adequate for review.

The overall safety profile and safety findings from MET during Years 6 and 7 are summarized below.

Adverse events:

- No deaths occurred.
- A total of 12 SAEs occurred in ten women (2.8%); five with onset in Year 6 and five with onset in Year 7. The five SAEs experienced by women in Year 7 are: one suicidal ideation (preceded by suicide attempt), ectopic pregnancy with contraceptive device, partial uterine perforation, embedded device, and obesity. The seven SAEs experienced by women in Year 6 are: suicidal ideation; pregnancy with spontaneous abortion; conversion disorder with radial nerve palsy; cerebellar stroke and vertebral artery dissection after neck injury; and volvulus. One SAE, suicide ideation preceded by suicide attempt was unresolved at time of data lock. Mirena was removed for both pregnancies and partial uterine perforation/embedded device.
- AEs leading to discontinuation occurred in 24 women (6.6%). The events include ectopic pregnancy (1), spontaneous abortion (1), vaginal/menstrual bleeding (10), device expulsion (5), partial uterine perforation/embedded device (2), dysmenorrhea (1), pelvic pain (1), uterine pain (1), dyspareunia (1), depression (1), irritability (1), premenstrual syndrome (1), vaginal infection (1), breast swelling (1), breast tenderness (1), and weight increased (1). More than one event occurred in some women. Most of the AEs are included in the Mirena label.
- AESI of partial uterine perforation/embedment and ectopic pregnancy occurred in less than 1% of women. Device expulsion was experienced by five women (1.4%). None of the ovarian cysts detected required treatment or lead to subject discontinuation and were not considered AEs. All the AESIs are included in the Mirena label.
- Common AEs occurring in >5% of women were vulvovaginal infections (9.9%); weight increase (6.4%); gastrointestinal, abdominal/pelvic pain (5.8%); anxiety reaction (5.2%); female genital tract bleeding (5.2%); and depression/depressed mood (5%). Except for anxiety reaction and weight gain, the remaining AEs are included in product labeling. Weight gain should be included in AEs experienced by women in the MET. Anxiety was reported in 23% of women at baseline, therefore the 5% reported anxiety reaction is unlikely to be due to an addition year of Mirena use.
- No clinically significant changes or trends occurred in laboratory parameters and vital signs, except for weight gain. As weight gain is a concern that women have when using contraception, this trend will be included patient and prescriber labeling.
- AE frequencies by demographic categories did not show clinically significant differences, although sample sizes were small in some subgroups.

Bleeding profile:

- The bleeding pattern during Years 6 and 7 of Mirena use remained stable. Approximately 25% of women experienced 90-days of amenorrhea. During 28-day cycles, about 60% of women experienced an average of 3 days of bleeding and spotting and 30% experienced bleeding only for an average of 1 day.

The overall safety findings from the "Patients Who Used a Single Mirena for >5 Years: Summary of Postmarketing Reports. Supplement with Reports Received Between May 9, 2019 and May 8, 2020" are summarized below:

- No increased frequencies of individual AEs by duration of use up to eight years of Mirena use
- Complication of device removal was the most common AE reported
- Device breakage occurs with complication of device removal (e.g., embedment)

In conclusion, the overall safety profile of findings from the MET clinical trial for Years 6 and 7 of Mirena use and collectively from the global safety database is acceptable and supports approval of Mirena for prevention of pregnancy for up to 7 years of use.

8.3. Statistical Issues

No statistical issues were noted in this supplementary NDA submission. The Division's conclusions on the efficacy were based on the pregnancy rate estimates from both PI (primary and sensitivity analysis) and supportive life table analysis using Kaplan-Meier method.

8.4. Conclusions and Recommendations

The overall efficacy and safety profile of Mirena IUS is acceptable and supports approval for prevention of pregnancy for up to 7 years of use.

9. Advisory Committee Meeting and Other External Consultations

No effectiveness or safety issues were identified during this team review that required expert advisory committee input.

10. Pediatrics

In accordance with PREA, the application for the new indication of contraception for duration of use up to seven years requires an assessment of the safety and effectiveness of Mirena IUS for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

On January 15, 2021, the Applicant submitted the PSP and proposed to address the PREA requirements for Mirena use up to seven years as follows:

- Partial waiver for boys and premenarchal girls (0-11 years of age) because contraception is not needed in this population.

(b) (6)

On June 8, 2020, the Pediatric Advisory Committee (PAC) met and approved the Applicant's PSP with the Agency's recommendations.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

The Applicant included revised proposed labeling in the submitted efficacy supplement. In consultation with the Associate Director of Labeling for DUOG, DMEPA (Baugh 2021), and other review disciplines, recommendations and revisions to the Applicant's proposed Prescriber Information (USPI) and the Patient Product Information (PPI).

Division of Medication Error Prevention and Analysis (DMEPA) assessed the supplement label and found the proposed revision to the Mirena IUS label acceptable (Baugh 2021).

The key revisions for the USPI are summarized in Table 29. Changes in the PPI were increasing use of Mirena up to 7 years.

Table 29. Key Labeling Changes for Supplement S-42

Section in USPI	Agreed Upon Text for Label	Explanation of Change
1.1: Indications and Usage Contraception	Mirena is indicated for prevention of pregnancy for up to 7 years; replace after the end of the seventh year.	Increased duration of contraceptive use based on findings from MET clinical study.
2.1: Dosing Over Time	This rate decreases progressively to approximately 10 mcg/day after 5 years and 8 mcg/day after 7 years. For contraception, remove Mirena by the end of the seventh year …	Added findings of LNG release rate after 7 years and need for removal by the end of the seventh year of Mirena use.
2.4: Removal of Mirena	Removal may be associated with: ●breakage or embedment of Mirena in the myometrium that can make removal difficult *[see Warnings and Precautions (5.5)]*. Analgesia, paracervical anesthesia, cervical dilation, alligator forceps or other grasping instrument, or hysteroscopy may be used to assist in removal.	Alert prescribers to reports of device breakage often occurring with difficult removal and mitigating actions
6.1 Clinical Trials Experience	A separate study of 362 women … showed a consistent adverse reaction profile in Years 6 and 7 as shown in Table 2. By the end of Year 7 of use, amenorrhea and infrequent bleeding are experienced by 28% and 26% of users, respectively; irregular bleeding occurs in 12%, frequent bleeding in 8%, and prolonged bleeding in 2% of users. In this study, 6% of women reported the adverse event of weight gain; it is unknown if the weight gain was caused by Mirena.	Included findings from MET on AEs and bleeding profile. Bleeding profile based on eighth 90-day reference period. Addition of weight gain as an AE.
14.1: Clinical Trials on Contraception	…, and the PI for the 7th year of use based on the 1 pregnancy that occurred during Year 7 and within 7 days after Mirena removal or expulsion and 2,912 evaluable cycles was 0.45 with a 95% upper confidence limit of 2.49. The cumulative 2-year pregnancy rate for Years 6 and 7 was estimated by the Kaplan-Meier method. Based on 2 pregnancies (1 in Year 6 and 1 in Year 7) and 7,269 exposure cycles, the cumulative pregnancy rate at the end of the 2-year period of extended use (Years 6 and 7) was 0.71% with a 95% upper confidence limit of 2.84%.	Efficacy data for the second year of the study presented as agreed upon in the SAP.

12. Risk Evaluation and Mitigation Strategies (REMS)

No safety issues were identified in this supplement application that would require initiation of a REMS.

13. Postmarketing Requirements and Commitment

None.

14. Deputy Division Director (Clinical) Comments

I concur with the clinical reviewer and CDTL that the submitted data is sufficient for approval. From an effectiveness perspective, the 7 year Pearl Index is favorable to extend use of Mirena to 7 years and the calculation was confirmed by the statistical review team. The safety profile for Mirena was also reviewed and found to be acceptable for an intrauterine system product. Updates to the prescription and patient labels will inform patients of the available data and the benefit/risk of this product. No REMS or other postmarketing requirements are needed

15. Appendices

15.1. References

Baugh, DV, 2021, Label, Labeling, and Packaging Review: NDA 21-225, S-042 Mirena (levonorgestrel-releasing intrauterine system), OSE RCM #2020-2227, FDA/CDER/OSE/OMEPRM/DMEPA, https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805e0ccf&_afrRedirect=1170653731723075.

Bayer HealthCare Pharmaceuticals, 2021a, Prescribing Information: Mirena, accessed June 11, 2021, https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021225s036lbl.pdf.

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World Health Organization, 2020, Family Planning/Contraception Methods Fact Sheet, June 11, 2021, https://www.who.int/news-room/fact-sheets/detail/family-planning-contraception.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Mirena Extension Trial, Protocol 18649 entitled "Multi-center, open-labeled, uncontrolled study to assess contraceptive efficacy and safety of Mirena during extended use beyond 5 years in women 18 to 35 years of age including a subgroup evaluation of treatment effect on heavy menstrual bleeding"

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 61		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): none		
If there are investigators with disclosable financial interests/arrangements, identify the		

number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) none		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

N/A

15.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

Population PK Analysis

The Applicant submitted an updated population PK analysis report entitled "BAY86-5028, Population PK analysis of the levonorgestrel releasing intrauterine system Mirena over 7 years and prediction up to 8 years (R-13456)." In this report, the Applicant updated the 6-year population PK model and the 6 year-release model by adding available 7-year data. The approach in this updated modeling analyses is same to the previous modeling analysis in R-19450 (see Section 19.4.1 in NDA 021225 Multi-Disciplinary Review and Evaluation review dated October 12, 2018, for details of the model and relevant information). The reviewer repeated and verified the Applicant's updated models and deems the analysis is acceptable. Updated results from the modeling and simulation analysis are summarized below (Tables 30, 31, 32, and 33.

Table 30. Summary Statistics of Total LNG Concentrations Estimated Based on the 7-Year PopPK Model at Representative Time Points During Mirena Use up to 7 Years for the Mirena Extension Trial Participants Only

Time after insertion	Number of women[b]	Geometric mean (ng/L)	Lower 95% CI	Upper 95% CI	Geometric CV (%)
15 days[a]	361	184	178	191	37.4
24 days[a]	361	179	172	185	36.7
1 month[a]	361	177	170	183	36.5
2 months[a]	361	173	167	179	36.2
3 months[a]	361	171	165	177	36.3
6 months[a]	361	167	161	174	36.3
9 months[a]	361	164	159	171	36.4
1 year[a]	361	162	156	168	36.5
2 years[a]	361	151	146	157	36.7
3 years[a]	361	141	136	147	36.9
4 years[a]	361	132	127	137	37.1
5 years	361	124	119	128	37.3
5.5 years	341	119	114	124	37.3
6 years	330	115	110	119	37.8
6.5 years	309	110	105	114	37.7
7 years	276	106	102	111	38.3

CI = confidence interval; CV = coefficient of variation; LNG = levonorgestrel
1 month = 30 days, 1 year = 365 days.
[a] estimation beyond minimum time of Mirena use of observed data for MET in dataset
[b] compared to previous analysis R-13075: two subjects less due to site closure; one subject which was omitted in the previous analysis due to withdrawal from study, was included in the 7-year analysis; one subject was excluded due to missing LNG concentrations

Source: Table 2-3 on page 14 of Summary of Clinical Pharmacology

Table 31. Summary Statistics of Unbound LNG Concentrations Estimated Based on the 7-Year PopPK Model at Representative Time Points During Mirena Use up to 7 Years for the MET Participants Only

Time after insertion	Number of women[b]	Geometric mean (ng/L)	Lower 95% CI	Upper 95% CI	Geometric CV (%)
15 days[a]	361	2.88	2.81	2.95	23.1
24 days[a]	361	2.82	2.75	2.88	23.0
1 month[a]	361	2.80	2.73	2.86	23.0
2 months[a]	361	2.74	2.68	2.81	23.0
3 months[a]	361	2.71	2.65	2.78	23.0
6 months[a]	361	2.65	2.59	2.72	23.0
9 months[a]	361	2.60	2.54	2.66	23.0
1 year[a]	361	2.55	2.49	2.61	23.0
2 years[a]	361	2.38	2.32	2.43	23.0
3 years[a]	361	2.22	2.16	2.27	23.0
4 years[a]	361	2.07	2.02	2.12	23.0
5 years	361	1.93	1.88	1.97	23.0
5.5 years	341	1.86	1.81	1.90	23.1
6 years	330	1.79	1.75	1.84	23.4
6.5 years	309	1.72	1.68	1.76	23.2
7 years	276	1.66	1.61	1.70	23.5

CI = confidence interval; CV = coefficient of variation; LNG = levonorgestrel
1 month = 30 days, 1 year = 365 days.
[a] estimation beyond minimum time of Mirena use of observed data for MET in dataset
[b] compared to previous analysis R-13075: two subjects less due to site closure; one subject which was omitted in the previous analysis due to withdrawal from study, was included in the 7-year analysis; one subject was excluded due to missing LNG concentrations

Source: Table 2-4 on page 15 of Summary of Clinical Pharmacology

Table 32. Model-Based Estimated In Vivo Release Rates of LNG From Mirena at Representative Time Points

Time after insertion	Typical in vivo release rate, µg/day	90% Confidence interval, µg/day
15 days	21.3	21.2 / 21.5
24 days	21.2	21.0 / 21.3
1 month	21.1	21.0 / 21.2
2 months	20.8	20.7 / 20.9
3 months	20.5	20.4 / 20.7
6 months	19.8	19.7 / 19.9
9 months	19.2	19.1 / 19.3
1 year	18.5	18.4 / 18.6
2 years	16.1	16.0 / 16.2
3 years	14.0	14.0 / 14.1
4 years	12.2	12.2 / 12.3
5 years	10.7	10.6 / 10.7
5.5 years	9.97	9.96 / 9.98
6 years	9.30	9.29 / 9.30
6.5 years	8.69	8.68 / 8.69
7 years	8.10	8.10 / 8.10
Average over 1st year of use	19.9	19.8 / 20.0
Average over 3 years of use	17.4	17.3 / 17.5
Average over 5 years of use	15.4	15.3 / 15.4
Average over 6 years of use	14.5	14.4 / 14.5
Average over 7 years of use	13.6	13.6 / 13.7

LNG = levonorgestrel
Calculations of the 90% confidence interval are based on 1000 simulations, considering the covariance matrix of the structural parameter estimates. The confidence interval is very narrow since only one parameter of the release model was re-estimated with low uncertainty.
1 month = 30 days, 1 year = 365 days.
Source: Table 2-7 on page 17 of Summary of Clinical Pharmacology

Table 33. Model-Based Estimated In Vivo Release Rates of LNG From Mirena, Kyleena, and Skyla

Time after insertion	Mirena[1] Typical [90% Confidence interval[3]] (µg/day)	Kyleena[2] Typical [90% Confidence interval] (µg/day)	Skyla[2] Typical [90% Confidence interval] (µg/day)
15 days	21.3 [21.2 / 21.5]	N/A	N/A
24 days[4]	21.2 [21.0 / 21.3]	15.4 [14.8 / 16.1]	13.4 [13.2 / 13.6]
1 year	18.5 [18.4 / 18.6]	9.90 [9.70 / 10.0]	5.93 [5.89 / 5.96]
2 years	16.1 [16.0 / 16.2]	8.60 [8.54 / 8.65]	5.61 [5.58 / 5.65]
3 years	14.0 [14.0 / 14.1]	8.07 [8.02 / 8.11]	5.51 [5.47 / 5.55]
4 years	12.2 [12.2 / 12.3]	7.78 [7.69 / 7.86]	N/A
5 years	10.7 [10.6 / 10.7]	7.59 [7.48 / 7.71]	N/A
5.5 years	9.97 [9.96 / 9.98]	N/A	N/A
6 years	9.30 [9.29 / 9.30]	N/A	N/A
6.5 years	8.69 [8.68 / 8.69]	N/A	N/A
7 years	8.10 [8.10 / 8.10]	N/A	N/A
Average over 1st year	19.9 [19.8 / 20.0]	12.1 [12.0 / 12.1]	8.04 [8.00 / 8.08]
Average over 3 years	17.4 [17.3 / 17.5]	9.83 [9.78 /9.86]	6.44 [6.42 / 6.46]
Average over 5 years	15.4 [15.3 / 15.4]	9.02 [8.98 / 9.04]	N/A
Average over 6 years of use	14.5 [14.4 / 14.5]	N/A	N/A
Average over 7 years of use	13.6 [13.6 / 13.7]	N/A	N/A

N/A = not applicable
Calculations of the 90% confidence interval are based on 1000 simulations, considering the covariance matrix of the structural parameter estimates.
1 year = 365 days
[1] Source: Module 5.3.3.5, R-13456
[2] Source: R-12970
[3] The confidence interval is very narrow since only one parameter of the release model was re-estimated with low uncertainty
[4] Due to the open ends of the hormone elastomer core for Kyleena and Skyla the initial LNG release (in vitro and in vivo) is much faster and variable and stabilizes only from day 24 onwards. Therefore, initial release for Skyla and Kyleena were only estimated from day 24 onwards
Source: Table 3-1 on page 20 of Summary of Clinical Pharmacology

15.5. Clinical Appendix

Table 34. Supplement Report: Summary Tabulation: Use >5 Years – All Adverse Events of Cases Included in the Analysis (N=224) Occurring in >5% of Reports, by Duration of Use[a,b,c]

Adverse event (MedDRA PT)	Duration of use													
	>5 to 5.25 yrs		>5.25 to 6 yrs		>6 to 7 yrs		>7 to 8 yrs		>8 yrs		>5 yrs NOS[d]		Total	
	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases	No of cases	% of cases
Complication of device removal	5	22.7%	18	24.7%	7	15.9%	5	23.8%	22	44.0%	2	14.3%	59	26.3%
Device breakage	4	18.2%	11	15.1%	4	9.1%	4	19.0%	13	26.0%	--	--	36	16.1%
Amenorrhoea	4	18.2%	8	11.0%	2	4.5%	6	28.6%	7	14.0%	--	--	27	12.1%
Device dislocation	2	9.1%	8	11.0%	5	11.4%	1	4.8%	5	10.0%	2	14.3%	23	10.3%
Embedded device	1	4.5%	4	5.5%	1	2.3%	4	19.0%	10	20.0%	1	7.1%	21	9.4%
Device difficult to use	2	9.1%	8	11.0%	4	9.1%	2	9.5%	3	6.0%	1	7.1%	20	8.9%
Device use issue	3	13.6%	5	6.8%	4	9.1%	1	4.8%	4	8.0%	2	14.3%	19	8.5%
Off label use of device	1	4.5%	6	8.2%	4	9.1%	1	4.8%	6	12.0%	--	--	18	8.0%
Genital haemorrhage	4	18.2%	5	6.8%	4	9.1%	2	9.5%	2	4.0%	--	--	17	7.6%
Device physical property issue	--	--	9	12.3%	3	6.8%	2	9.5%	3	6.0%	--	--	17	7.6%
Device expulsion	1	4.5%	7	9.6%	3	6.8%	--	--	5	10.0%	--	--	16	7.1%
Complication of device insertion	1	4.5%	4	5.5%	5	11.4%	2	9.5%	--	--	1	7.1%	13	5.8%
Procedural pain	2	9.1%	2	2.7%	4	9.1%	--	--	4	8.0%	1	7.1%	13	5.8%

Source: Submission NDA 21225, SDN 1874 received May 21, 2021, Appendix 1 – Version 2 – correct in response to FDA Clinical Information request of 17 May 2021.
[a] Excluding terms coding prolonged use
[b] Percentages are number of cases with AE/total number of cases in the respective duration of use category
[c] Sums may exceed total number of cases/100% because more than one AE/device issue might have been reported in a case
[d] Cases reporting use of >5 years but with insufficient information to allow further classification of duration

Clinical Review of Center for Devices and Radiologic Health (CDRH) Memorandum

NDA	**21225**
Applicant	**Bayer**
Drug	**Mirena (levonorgestrel-releasing intrauterine system)**
Indication	**Prevention of Pregnancy**
Reviewer	**Abby Anderson, MD** **Medical Officer, Division of Urology, Obstetrics and Gynecology (DUOG)**
Materials Reviewed	**● Memorandum from CDRH dated June 30, 2021[4]** **● Memorandum from Office of Surveillance and Epidemiology (OSE) dated June 14, 2021[5]**

Background

Mirena is a levonorgestrel-releasing intrauterine system (LNG IUS) initially approved for prevention of pregnancy for up to 5 years on December 6, 2000 and treatment of heavy menstrual bleeding in women who choose to use intrauterine contraception for up to 5 years

[4] Veronica Price, Biomedical Engineer, OPEQ/OHT3/DHT3B/THT3B3 dated June 30, 2021.
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805ff2a8&_afrRedirect=2636734570709122
[5] Miriam Chehab, PharmD, BCPPS. Dated June 14, 2021.
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805f973f&_afrRedirect=1701902148556988

on October 1, 2009. (b) (4) On August 20, 2020, the contraceptive indication for Mirena was extended to up to 6 years after approval of efficacy supplement S-040. On October 13, 2020, efficacy supplement S-042 was submitted to extend Mirena use for contraception up to 7 years. S-042 is currently under review. Postmarketing reports of adverse events (AE) occurring with use of Mirena for more than five years were included in the submission. During evaluation of postmarketing reports, sliding and breakage of the hormone reservoir during device removal was noted. Included in some of these reports was a Quality-Safety Evaluation comment of "After a couple years of use, the hormone cylinder loses some percentage of its hormone content and thus becomes slightly less firmly attached on the vertical part of Mirena. Therefore, it is possible though rarely encountered, that the hormone cylinder slides towards or over the T-body arms during the removal procedure if the cervical canal is very tight or the IUS is imbedded in the myometrium, and thus the removal procedure is difficult".[6]

The Division with input from CDRH and Office of Pharmaceutical Quality (OPQ) generated a list of items to elicit additional information on the hormone cylinder sliding and device breakage from the Applicant. A response to this information request (IR) was received from the Applicant on June 4, 2021.[7] CDRH provided a memorandum dated June 30, 2021 after evaluation of the additional information.[8]

This memorandum reviews the Applicant's response to the IR and summarizes the pertinent findings related to the hormone reservoir sliding and breakage as reported in the postmarketing reports of adverse events (AE) submitted with S-042. During the S-042 review cycle, OSE completed an update of their previous review on device breakage, and the related findings are also summarized in this memorandum.

Review

The Applicant's response to the IR included a description of the manufacturing process, quantified changes of the hormone cylinder and tensile strength over time, provided schematic of where device breakage occurred, listed the duration of use in cases with hormone reservoir sliding reported in S-042 postmarketing reports, results of risk management activities completed, a description of the manufacturing process and how it may relate to device event, expected and observed frequency and severity of the reported event, and any design manufacture in changes to the product since initially introduced.

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[6] NDA 21225 SDN 1800. Supplement: Patients Who Used a Single Mirena for > 5 Years: Summary of Postmarketing Reports. FAERS report 2020-021343 p 71 of 108

[7] NDA 21225. SDN 1881. Quality/Response to Information Request. Received June 4, 2021. \\CDSESUB1\evsprod\nda021225\0194\m1\us\12-cover-letters\response-to-cmc-information-request-dated-20may2021.pdf

[8] CDRH Memorandum. Veronica Price, Biomedical Engineer. Dated June 30, 2021. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805ff2a8&_afrRedirect=1702022599591252

The Applicant provided a table of the 14 reports related to hormone cylinder sliding from the S-042 submission with duration of IUS time provided. Based on this limited information, there does not appear to be a time point after which hormone reservoir sliding occurs more frequently.
The Applicant calculated the frequency of hormone reservoir complaints to be 9.5 per 1 million based on (b) (4) complaints related to the hormone cylinder and using sales data for 2020 as the denominator. The frequency of the events related to the hormone reservoir are "improbable" per ISO 14971.

CDRH memorandum

Veronica Price, CDRH Biomedical Engineer also noted the frequency of hormone reservoir related events is rare based on the Applicant's calculations and that from the information provided, there is no "clustering" of the issues around a certain time period or worsening over time.
CDRH is conducting further evaluations of device issues identified with the information provide. However, these evaluations are being conducted outside the S-042 review.

OSE memorandum

OSE reported device breakage identified in the FDA Adverse Event Reporting System (FAERS) database for all five FDA-approved IUSs. For Mirena, the random sampling case series performed in both the 2018 and 2021 reports noted an increased frequency of device breakage, including events involving the hormone reservoir occurred primarily upon removal. Stratified by years of use, device breakage was most frequent at five years and less than one year of Mirena use. Half of the device breakage reports contained reports of embedment, uterine perforation, or some resistance or difficulty with Mirena removal.

Conclusion

Based on the findings above, the events of hormone reservoir sliding/breakage/missing do not appear to occur more frequently with extended Mirena use. Rather, device breakage including hormone reservoir events is primarily recognized at time of removal and often reported with embedment, uterine perforation, or some resistance or difficulty with removal. For the purposes of this supplement CDRH did not identify any specific issues that need to be addressed before approval of this supplement.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ZETA-MAE C WILLIAMSON
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